Accepted Manuscript

Submission Date: 2024-02-08
Accepted Date: 2024-08-28
Accepted Manuscript online: 2024-08-29

Experimental and Clinical Endocrinology & Diabetes

A single sauna session does not improve postprandial blood glucose handling in individuals with type 2 diabetes mellitus: a cross-over, randomized, controlled trial

Laura Schenaarts, Floris K Hendriks, Cas J Fuchs, Wendy E Sluijsmans, Tim Snijders, Luc J van Loon.

Affiliations below.

DOI: 10.1055/a-2406-4491

Please cite this article as: Schenaarts L, Hendriks F K, Fuchs C J et al. A single sauna session does not improve postprandial blood glucose handling in individuals with type 2 diabetes mellitus: a cross-over, randomized, controlled trial. Experimental and Clinical Endocrinology & Diabetes 2024. doi: 10.1055/a-2406-4491

Conflict of Interest: The authors declare that they have no conflict of interest.

Trial registration: NCT05610046, ClinicalTrials.gov (http://www.clinicaltrials.gov/), Randomized, controlled trial

Abstract:
Introduction Passive heat treatment has been suggested to improve glycaemic control in individuals with type 2 diabetes mellitus. Previous studies have predominantly focused on hot water immersion and traditional sauna bathing, as opposed to the more novel method of infrared-based sauna bathing. Here we assessed the impact of a single infrared sauna session on post-prandial glycaemic control in older individuals with type 2 diabetes mellitus.
Methods In this randomized controlled crossover trial, 12 participants with type 2 diabetes mellitus (male/female: 10/2, age: 69±7 y, BMI: 27.5±2.9 kg/m²) rested in an infrared sauna twice: once in a heated condition (60°C) and once in a thermoneutral condition (21°C) for 40 min, immediately followed by a 2-h oral glucose tolerance test (OGTT). Venous blood samples were obtained to assess plasma glucose and insulin concentrations and to determine the whole-body composite insulin sensitivity index.
Results Body core and leg skin temperature were higher following the heated condition compared to the thermoneutral condition (38.0±0.3 vs 36.6±0.2°C and 39.4±0.8 vs 31.3±0.8°C, respectively; P<0.001 for both). The incremental area under the curve (iAUC) of plasma glucose concentrations during the OGTT was higher after the heated condition compared to the thermoneutral condition (17.7±3.1 vs 14.8±2.8 mmol/L/120 min; P<0.001). No differences were observed in plasma insulin concentrations (heated: 380±194 vs thermoneutral: 376±210 pmol/L/120 min; P=0.93) or whole-body composite insulin sensitivity indexes (4.5±2.8 vs 4.5±2.1; P=0.67).
Conclusions A single infrared sauna session does not improve postprandial blood glucose handling in individuals with type 2 diabetes mellitus. Future studies should assess the effect of more prolonged application of infrared sauna bathing on daily glycaemic control.

Corresponding Author:
Prof. Luc J van Loon, Maastricht University School of Nutrition and Translational Research in Metabolism, Department of Human Biology, Universiteitssingel 50, 6200 MD Maastricht, Netherlands, l.vanloon@maastrichtuniversity.nl

Affiliations:
Laura Schenaarts, Maastricht University School of Nutrition and Translational Research in Metabolism, Department of Human Biology, Maastricht, Netherlands

Floris K Hendriks, Maastricht University School of Nutrition and Translational Research in Metabolism, Department of Human Biology, Maastricht, Netherlands
Cas J Fuchs, Maastricht University School of Nutrition and Translational Research in Metabolism, Department of Human Biology, Maastricht, Netherlands
[...]
Luc J van Loon, Maastricht University School of Nutrition and Translational Research in Metabolism, Department of Human Biology, Maastricht, Netherlands

Table 1. Participant characteristics

	Participants (n = 12)
Age (y)	69 ± 7
Sex	
Female	2
Male	10
Body mass (kg)	83.4 ± 12.2
Height (m)	1.74 ± 0.10
BMI (kg/m^2)	27.5 ± 2.9
Fat free mass (kg)	33.0 ± 5.4
Fat mass (kg)	23.8 ± 5.9
Fat percentage (%)	28.5 ± 4.9
Time since onset T2DM (y)	12 ± 7
HbA1c (mmol HbA1c/mol Hb)	55.0 ± 7.1
HOMA-IR	2.4 ± 1.3
Number of hypoglycaemic agents	2.0 ± 0.6
Metformine	11
SGLT2-inhibitors	3
DPP4-inhibitors	3
Sulfonylureum derivates	7

Values are expressed as means ± SDs. BMI: body mass index. HbA1c: Hemoglobin A1c. T2DM: type 2 diabetes mellitus. HOMA-IR: Homeostatis Model Assessment for Insulin Resistance.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a metabolic disorder characterized by poor glycaemic control. Prolonged postprandial hyperglycaemia is a major risk factor for the development of microvascular complications and cardiovascular disease [1]. Forty-five percent of individuals with T2DM fail to achieve recommended blood glucose levels (HbA1c < 53 mmol HbA1c/mol Hb) [2]. Though lifestyle-based regimens can effectively improve glycaemic control in T2DM [3], adherence to such regimens is generally low [4, 5]. Therefore, additional strategies are required to improve glycaemic control in individuals with T2DM.

Passive heating has been proposed as a potential additional approach due to some similarities with low-intensity exercise [6]. This is interesting in the context of T2DM, considering that exercise is a well-established non-pharmacological intervention known to improve glycaemic control in this population [3, 7]. Physiological changes induced by physical exercise, such as increased heart rate, body temperature, sweat rates, and peripheral blood flow are also observed during heat stress [8, 9]. These thermoregulatory responses are crucial for maintaining physiological core temperatures in acute heat stress [8, 10]. Despite previous assumptions that thermoregulatory vasodilation exclusively occurs cutaneously [11] heat stress also induces a concomitant elevation in skeletal muscle blood flow [9, 12, 13]. As this may promote insulin-mediated glucose uptake in skeletal muscle tissue [14], passive heat treatment can potentially enhance postprandial peripheral glucose uptake in individuals with T2DM.

Despite its theoretical benefits, studies using a single session of hot water immersion as the passive heat modality have so far failed to observe any improvements in postprandial glucose concentrations and insulin sensitivity in individuals with T2DM [15-17]. Given that different heating modalities have shown distinct effects on physiological outcomes (e.g. body

temperature) [18, 19] highlights the importance of evaluating different passive heat modalities on health-related outcomes [20]. Unlike hot water immersion, in which heat is transferred through the skin, infrared sauna utilizes infrared waves that penetrate beyond the superficial layers of skin [21] thereby facilitating a more targeted heating effect of deeper tissues. Hence, this may augment peripheral skeletal muscle temperature and improve muscle perfusion more effectively. As a result, infrared sauna could be a beneficial heat treatment modality to improve peripheral glucose uptake in individuals with T2DM. To date, no studies have assessed how infrared sauna bathing acutely affects postprandial glycaemic excursions in individuals with T2DM.

The present study investigates the impact of a single infrared sauna bathing session on glycaemic excursions during a subsequent oral glucose tolerance test in individuals with T2DM. We hypothesized that infrared sauna bathing lowers postprandial glycaemic excursions in comparison with a thermoneutral control condition in individuals with T2DM.

METHODS

Participants

Twelve men and women with T2DM of at least 50 y old and using at least one oral hypoglycaemic agent were recruited to participate in the current study via advertisements (**Table 1**). Exclusion criteria included insulin usage, recent changes in diabetes medication, frequent (≥1 time/week) use of sauna, participation in a structured exercise program in the past 3 months, >5% weight change over the past 6 months, inability to tolerate high temperatures, smoking, and diagnosis of medical condition(s) that could jeopardize participant safety or hinder data interpretation.

All participants were fully informed regarding the experimental procedures and associated risks. Remaining questions were answered before written informed consent was obtained. The study was conducted in accordance with the principles outlined in the Declaration of Helsinki and was approved by the Medical Research Ethics Committee Academic Hospital Maastricht/Maastricht University (METC 22-057). The study was registered on ClinicalTrials.gov (NCT05610046).

Study design

The present counterbalanced randomized cross-over controlled trial was conducted at the Department of Human Biology, Maastricht University, The Netherlands, between February 2023 and April 2023 to minimize natural heat acclimatization. Participants were randomly allocated to start with the HOT or CON experimental condition by an independent researcher according to a block randomization plan using an online block randomizer (http://www.randomization.com). Participants underwent the HOT and CON conditions in a counterbalanced order: at rest in a seated position in an infrared sauna (HM-LSE-3 Professional edition, Health Mate, Belgium) at 60°C (humidity is not controlled in an infrared

sauna) for 40 min (HOT) and in thermoneutral conditions at 21°C for 40 min (CON), immediately followed by a 7-point OGTT to determine postprandial glycaemic excursions. Outcome parameters included plasma glucose and insulin concentrations, tympanic and skin temperature, haematocrit, blood pressure, and heart rate. Experimental trials were completed with a wash-out period of at least 7 days between visits to limit acclimation effects. Humidity in the laboratory was 64±2.7%.

Screening

All participants were invited to the laboratory for a screening visit to assess eligibility for the study. Participants arrived in the laboratory in a fasted state and without consumption of their morning hypoglycaemic medication. Medical history was assessed and heart and lungs were auscultated by a qualified physician. Subsequently, body mass and height, resting blood pressure, and resting heart rate were measured. A multi-frequency bioelectrical impedance analyser *(*InBody-S10; Biospace, Cerritos, CA, USA*)* was used according to the manufacturer's guidelines for the estimation of body composition. Lastly, all participants were familiarized with infrared sauna bathing at 60°C for 30 min.

Instructions prior to test days

Throughout the two days prior to the experimental procedures participants were instructed to maintain their habitual diet and activity levels, refrain from strenuous physical activities, and avoid alcohol consumption. A standardized meal (~3000 kJ, providing 54 energy percent (en %) carbohydrates, 27 en% fat, and 16 en% protein) was consumed before 10:00PM prior to each test day, and followed by an overnight fast. On the morning of each test day, participants did not consume any hypoglycaemic medication. Food intake was recorded in two-day food diaries before both test days to allow replication and check for differences between test days. Food intake records were summarized based on the Dutch food

composition table NEVO 2021 [22] and described as total energy intake (kJ), total carbohydrate, total protein, and total fat intake (En%).

Experimental visits

An overview of the experimental protocol is depicted in **Figure 1**. Participants reported to the laboratory between 08:00 and 09:00AM, after which resting blood pressure, body mass, and tympanic temperature (as a measure for core temperature) were measured. Subsequently, a heart rate monitor was adjusted around the chest and skin thermometers (iButton, Maxim Integrated Products, San Jose, CA, USA) were applied on both upper legs to continuously measure heart rate and skin temperature, respectively, throughout the test day. Tympanic temperature was measured using a tympanic thermometer (Braun ThermoScan IRT 6520, Kronberg, Germany) with each blood collection. After baseline measurements, a cannula was inserted into an antecubital vein. Following pre-sauna blood sampling (baseline, t=-40 min), participants entered the infrared sauna and remained seated for 40 min in the HOT or CON condition, wearing underwear only. Directly after exiting the sauna, tympanic temperature and blood pressure were measured. After removing all sweat from the body, body mass was determined. A blood sample (t=0 min) was collected before consumption of the glucose beverage containing 75 g glucose dissolved in 200mL water (LemonGluc, Novolab, Belgium), after which participants were allowed to drink 100 mL of water. The 2-h OGTT commenced within 10 min after exiting the sauna. During the OGTT, participants remained seated (were allowed to read) and wore clothing of choice. Additional blood samples were obtained at t=15, 30, 45, 60, 90, and 120 min. Blood pressure and body mass were measured again following the final blood draw.

Blood analysis

On the first test day, one blood sample was collected at baseline in a heparin-containing tube for HbA1c analysis, while all other blood samples were collected in EDTA-containing tubes. Homogenized blood was collected into 3 heparinized micro-haematocrit capillary tubes, centrifuged (5 min at 8500*g* at 21°C) and subsequently, haematocrit values were determined. Thereafter, remaining blood was centrifuged (10 min at 1000*g* at 4°C) to obtain plasma. Aliquots of plasma were frozen in liquid nitrogen and stored at -80°C until analysis of plasma glucose, insulin, noradrenaline, and cortisol concentrations using commercially available kits (glucose HK CP, ABX Diagnostics, Montpellier, France; Human Insulin ELISA, Meso Scale Discovery, Rockville, Maryland, USA; TECAN ELISA, IBL International GmbH, Hamburg, Germany, respectively).

Insulin sensitivity indices

Plasma glucose and insulin concentrations throughout the 7-point OGTT were used to calculate the whole-body composite insulin sensitivity index ($ISI_{composite}$) as defined by Matsuda and DeFronzo [23], as shown in the formula below:

where G_0 and I_0 represent fasting post-sauna (t=0 min) plasma glucose (mg/dL) and insulin (mUi/L) concentrations, respectively. G_{mean} and I_{mean} represent time-weighted means of plasma glucose and insulin concentrations during the OGTT. Additionally, tissue-specific insulin sensitivity indices including the hepatic insulin resistance index (HIRI) and muscle insulin resistance index (MISI) [24] were calculated. HIRI and MISI were calculated using the formulas as shown below:

The incremental area under the curve (iAUC) for plasma glucose and insulin concentrations during the OGTT were calculated based on the trapezoid method, using fasting post-sauna plasma glucose (mmol/L) and insulin (pmol/L) concentrations as baseline. The Homeostatis Model Assessment for Insulin Resistance (HOMA-IR) [25] was determined from fasting pre-sauna plasma glucose (mg/dL) and insulin (mUi/L) concentrations.

Statistics

All data were tested for normality using the Shapiro-Wilk test ($P<0.05$). Wilcoxon Signed-Rank test was used for not normally distributed data of $ISI_{composite,}$ HIRI and MISI. A paired samples T-test was used to analyse the iAUC of plasma glucose and insulin. Time-dependent outcomes (i.e. plasma glucose and insulin concentrations, noradrenaline and cortisol concentrations, haematocrit, tympanic and skin temperature, heart rate, and blood pressure) were analysed using two-way (time × condition) repeated measures ANOVAs. If a significant time effect was observed, Bonferroni post-hoc corrections were applied to localize differences between time-points. In case of a significant interaction, separate one-way repeated measures ANOVA analyses were performed for HOT and CON to locate significant differences between time-points and paired samples T-tests were used to analyse differences between HOT and CON at all time-points. T-tests were not corrected for multiple comparisons. Correlations were explored between plasma noradrenaline and cortisol concentrations and iAUC of plasma glucose and insulin during HOT and CON for time points t=-40, t=0, and t=60 min using Pearson's correlation coefficients. Significance was set at $P<0.05$. Normally distributed data are presented as means ± SDs and not normally distributed data as medians with [95% confidence intervals]. Statistical analyses were performed using the statistical software program IBM SPSS (version 28.0, IBM Corp., Armonk, NY, USA).

RESULTS

Participant characteristics

Participant characteristics are depicted in **Table 1.** All participants completed both test days. No adverse effects were reported.

Thermoregulatory response

Tympanic and skin temperature were not different at baseline in HOT (P=0.384) and CON (P=0.157), **Figure 2A-B**. A significant time × condition interaction was observed for tympanic and skin temperature (P<0.001 for both). Between baseline and t=0 min (pre- to post-sauna) in HOT, tympanic temperature increased (P<0.001). Likewise, skin temperature in HOT increased from baseline to t=0 min (P<0.001). No changes in tympanic and skin temperature over time were observed for CON (P>0.05). At t=0 min, tympanic and skin temperature were higher in HOT compared to CON (P<0.001 for both). Compared to CON, tympanic temperature in HOT remained elevated until t=60 min (P<0.05 for all), while skin temperature remained higher until t=90 min (P<0.05 for all).

Plasma glucose and insulin concentrations

Plasma glucose concentrations at baseline were not different between HOT and CON (P=0.81, **Figure 3A**). Plasma glucose concentrations did not differ between baseline and t=0 min in HOT (P=1.0) and CON (P=1.0). A significant time × condition interaction was found for plasma glucose concentrations throughout the test day (P<0.001). Plasma glucose concentrations increased following glucose ingestion and remained elevated until the end of the test day in both conditions (P<0.001 for all values after t=0 min). From t=15 to t=120 min, plasma glucose concentrations were higher in HOT compared to CON (P<0.05 for all). The iAUC of plasma glucose concentrations (P<0.001) and peak plasma glucose concentrations (P<0.001) were higher in HOT when compared to CON. A significant effect

of time (P<0.001), but not condition (P=0.92) was observed for plasma insulin concentrations throughout the test days (**Figure 3C**). Compared to t=0 min, plasma insulin concentrations were significantly higher at t=15, 45, 60, 90, and 120 min in HOT (P<0.05 for all) and t=15, 60, 90, and 120 min in CON (P<0.05 for all), with no difference between the two groups (time × condition interaction, P=0.059). Insulin iAUC did not differ between conditions (P=0.93). Haematocrit at baseline was 43.0±3.1 and 42.5±3.6 % during the HOT and CON condition, respectively, and did not differ between conditions or over time (time: P=0.60; condition: P =0.60; time × condition: P=0.15). When plasma glucose and insulin values were corrected for haematocrit, similar outcomes were observed (Supplementary figure 1).

Insulin sensitivity indices

No differences were observed between HOT and CON for $ISI_{composite}$ (P=0.67), HIRI (P=0.39), and MISI (P=0.73), as depicted in **Figure 4**.

Cardiovascular response

Heart rate was not recorded for n=1 during CON due to technical malfunctioning of the heart rate monitor. Heart rate did not differ at baseline between conditions (P=0.63, **Figure 2C**). A significant time × condition interaction was found for heart rate (P<0.001). Heart rate increased between baseline and t=0 min in HOT (P=0.04), while no changes over time were observed for CON (P=1.0). Heart rate was higher in HOT than in CON between t=-30 and t=15 min (P<0.05 for all).

Systolic blood pressure (SBP) at baseline was not different in HOT and CON (144±13 and 144±13 mmHg; P=1.0, Supplementary figure 2). A main effect of time (P=0.005), but not condition (P=0.139) was observed for SBP. SBP in HOT and CON combined decreased from 144±13 at baseline to 133±19 mmHg at t=0 (P=0.008), with no difference between the two groups (time × condition interaction, P=0.222). Diastolic blood pressure (DBP) was not

different between HOT and CON at baseline (78±6 vs 79±7 mmHg; P=0.61). DBP showed a significant time × condition interaction (P=0.013). During HOT, DBP decreased from 78±6 to 63±11 mmHg between baseline and t=0 (P<0.001) and did not return to baseline at t=120 (72±11 mmHg; P=0.011), while no changes over time occurred in CON. DPB was lower in HOT compared to CON at t=0 min (63±11 vs 77±12 mmHg; P=0.005) and t=120 min (72±11 vs 79±14 mmHg; P=0.021).

Catecholamines

Noradrenaline and cortisol concentrations did not differ between HOT and CON at baseline (P>0.05, **Figure 5**). A significant time × condition interaction was found for both noradrenaline and cortisol concentrations (P<0.001). In HOT, noradrenaline concentrations increased between baseline and t=0 min (P<0.001) and returned to baseline at t=60 min (P=1.0), while cortisol concentrations did not change over time (P=1.0). In CON, noradrenaline concentrations remained unchanged between baseline and t=0 min (P=0.378), whereas cortisol concentrations decreased (P<0.001). Noradrenaline concentrations in CON increased from baseline to t=60 (P=0.017), while cortisol concentrations returned to baseline (P=1.0). At t=0 min, noradrenaline and cortisol concentrations were higher in HOT compared to CON (P<0.05). At t=60 min, noradrenaline concentrations were lower in HOT compared to CON (P=0.020), while cortisol concentrations did not differ between HOT and CON (P=0.64). A positive correlation was found in CON between glucose iAUC and cortisol concentrations at t=0 (Pearson's r=0.617; P=0.033). Furthermore, a tendency towards a positive correlation was observed in HOT between glucose iAUC and noradrenaline concentrations at t=0 min (Pearson's r=0.560; P=0.058, Supplementary figure 3).

Body mass

A significant time × condition interaction was observed for body mass (P<0.001). During HOT, body mass decreased from 82.7±12.1 to 82.4±12.1 kg between baseline and t=0 min (P<0.001) and did not return to baseline values at t=120 (82.5±12.1 kg; P=0.022). In CON, body mass was 83.2±12.4 kg at baseline and did not change throughout the test day.

Dietary intake

During the two days prior to HOT and CON, no differences were observed in average daily intake of dietary energy (84±24 vs 80±20 kJ/kg/d; P=0.52), carbohydrate (43±4 vs 44±7 En %; P=0.58), protein (18±3 vs 19±3 En%; P=0.26) and fat (39±5 vs 37±6 En%; P=0.28).

DISCUSSION

The present study shows a greater postprandial rise in circulating plasma glucose concentrations following glucose ingestion after a single session of infrared sauna bathing when compared to a thermoneutral condition in individuals with T2DM, with no differences in circulating plasma insulin concentrations. In contrast to our hypothesis, a single session of infrared sauna bathing did not result in lower blood glucose excursions following glucose ingestion in individuals with T2DM.

In line with previous work on passive heat treatment [15, 17, 26-31], we showed that infrared sauna bathing increased tympanic temperature, skin temperature, and heart rate (Figure 2A-C). These physiological changes, though varying in magnitude, show some similarities to those elicited by low intensity exercise [6]. It has been well established that exercise increases skeletal muscle blood flow, which partly contributes to an increased glucose uptake in people with T2DM [3, 7]. Given that infrared sauna bathing may also potently stimulate skeletal muscle blood flow, we hypothesized that a single session of infrared sauna bathing lowers glucose excursions during a subsequent oral glucose tolerance test in adults with T2DM. However, we observed a more (instead of less) pronounced postprandial rise in circulating plasma glucose concentrations, with no changes in insulin concentrations and insulin sensitivity, during the 2-h OGTT that was performed immediately following infrared sauna bathing when compared to the same treatment in a thermoneutral condition (Figure 3A, 3C and 4, respectively). Our data are in contrast with previous studies showing no impact of a single session of passive heat treatment (i.e. hot water immersion) on postprandial glucose concentrations and/or insulin sensitivity in individuals with T2DM [15-17]. However, it is important to note that previous studies in non-diabetic populations have also observed increased (instead of reduced) postprandial glucose concentrations with acute passive heat treatment compared to thermoneutral control settings [28-30, 32, 33]. Taken together, our

study adds to the existing literature suggesting that a single session of passive heat treatment does not facilitate a reduction in postprandial glucose concentrations or an improvement in insulin sensitivity [15-17, 28-30, 32, 33].

Several mechanisms can be explored to elucidate the observed greater, instead of a lesser, post-prandial rise in circulating plasma glucose concentrations. We explored whether a decline in blood volume through sweating might explain the more elevated post-prandial blood glucose concentrations following passive heat treatment. Participants lost 300±100 mL of body mass following passive heating, while no decline in body mass was observed in the thermoneutral condition. However, no significant changes were observed in blood haematocrit levels over time or between treatments. In line with previous work investigating the impact of hypohydration on glycaemic excursions [34], we did not detect any differences in plasma glucose data when data were corrected for blood sample haematocrit values. The initial elevation in plasma glucose concentrations may also be (partly) attributed to arterialization of venous blood samples after heating [35, 36]. Nevertheless, it has been shown that the arterialization effect of local hand heating disappears within ~15 min after removing the heat source [37]. How long this effect persist after whole-body heating is not known, though it is unlikely that arterialization explains the prolonged elevation in glucose concentrations observed up until 2 hours after exiting the sauna.

As skin and tympanic temperature and heart rate increased, it seems reasonable to assume that peripheral blood flow was increased following passive heat treatment[9]. However, greater peripheral blood flow did not result in an increase in peripheral blood glucose uptake, or at least insufficient to attenuate post-prandial blood glucose excursions. Therefore, we speculate that increased muscle perfusion during heat stress primarily facilitates heat dissipation to the skin, rather than improving peripheral glucose uptake in skeletal muscle. Furthermore, heat stress-induced release of stress hormones may have stimulated hepatic

glucose output, leading to an elevation in endogenous glucose appearance [9, 31, 38, 39]. In accordance, we observed an elevation in plasma noradrenaline and cortisol concentrations measured immediately following infrared sauna bathing and also observed a tendency towards a positive correlation between glucose iAUC and noradrenalin concentrations after infrared sauna bathing. This implies that a systemic stress response may have contributed to the observed elevation in postprandial blood glucose concentrations in this study. Finally, it could be that during heat stress blood is redirected from splanchnic region to accommodate increased skin perfusion [40], potentially slowing gastric emptying and, as such, glucose absorption. Speculatively, this may also account for the prolonged postprandial elevation of blood glucose concentration.

Although a relatively small sample size was included, the robust cross-over study design allowed us to reliably detect relevant differences in body and skin temperature between the two conditions. Unfortunately, we were not able to measurements of rectal temperature and/or skin temperature at multiple body site to provide a more accurate assessment of body temperature during and following passive heat treatment. Also, composite indicators of whole-body insulin sensitivity are not as reliable as measurements using the gold standard hyperinsulinemic-euglycaemic clamp and glucose tracers. Therefore, to understand glucose fluxes and insulin action following heat treatment, future work that directly measures glucose fluxes is warranted. It is worth noting that the present study should be regarded as a proof-of-principle, as the study design applied in the present study does not apply to normal, daily life conditions. Participants ingested 75 g glucose within 5 min for the OGTT following the passive heat treatment and control condition. Administration of such high glucose loads result in more rapid glucose absorption compared to the gradual absorption of glucose following ingestion of a normal mixed meal [41]. The timing of heat treatment, however, does not seem to impact subsequent post-prandial blood glucose responses. To illustrate, no differences

were observed between glycaemic excursions when performing the OGTT either during or 30 min after hot water immersion in individuals with T2DM [17]. Moreover, no differences in glycaemic excursions were seen 1 h [15] or 24 h [16] after hot water immersion in individuals with T2DM.

Interestingly, in contrast to the outcomes of most studies addressing the acute impact of heat treatment, prolonged passive heat treatment has consistently been found to improve glycaemic excursions in healthy [42], overweight [26, 43] and individuals with T2DM [44]. It seems that the thermal stress through repeated acute passive heating triggers adaptations that may improve thermoregulation in challenging environments. At present, the effects of prolonged application of frequent infrared sauna bathing on glycaemic outcomes in T2DM remain to be investigated.

In conclusion, a single session of infrared sauna bathing does not attenuate the postprandial rise in circulating blood glucose concentrations during a subsequent oral glucose tolerance test in individuals with T2DM. Future work should focus on identifying underlying mechanisms by directly measuring glucose fluxes, investigating hormonal influences, and blood flow distribution to further explore the effects of different modalities of acute and more chronic passive heat treatment on glycaemic excursions and cardiovascular risk factors in individuals with T2DM.

AUTHOR DISCLOSURES

None of the authors have any conflicts of interest to declare.

AUTHOR CONTRIBUTIONS

LS: conceptualization, methodology, software, formal analysis, investigation, data curation, writing – original draft, visualization, project administration. **FK**: conceptualization, methodology, software, validation, investigation, writing – review & editing, supervision, project administration. **TS**: conceptualization, methodology, writing – review & editing, supervision. **CF**: resources, writing – review & editing, supervision. **WS**: resources, writing – review & editing. **LvL**: conceptualization, methodology, writing – review & editing, supervision.

ACKNOWLEDGEMENTS

The authors highly appreciate the technical expertise of Hasibe Aydeniz during the sample analysis. The authors also appreciate the practical assistance from Antoine Zorenc, Joan Senden, Thimo de Winter, and Mats te Bos. We thank HealthMate for the supply of the infrared sauna for this study.

REFERENCES

1. Laakso M. Hyperglycemia and cardiovascular disease in type 2 diabetes. Diabetes. 1999;48(5):937-42.

2. Polonsky WH, Henry RR. Poor medication adherence in type 2 diabetes: recognizing the scope of the problem and its key contributors. Patient Prefer Adherence. 2016;10:1299-307.

3. Colberg SR, Sigal RJ, Fernhall B, et al. Exercise and type 2 diabetes: the American College of Sports Medicine and the American Diabetes Association: joint position statement. Diabetes Care. 2010;33(12):e147-67.

4. Stutts WC. Physical activity determinants in adults. Perceived benefits, barriers, and self efficacy. Aaohn j. 2002;50(11):499-507.

5. Praet SFE, van Rooij ESJ, Wijtvliet A, et al. Brisk walking compared with an individualised medical fitness programme for patients with type 2 diabetes: a randomised controlled trial. Diabetologia. 2008;51(5):736-46.

6. Cullen T, Clarke ND, Hill M, et al. The health benefits of passive heating and aerobic exercise: To what extent do the mechanisms overlap? J Appl Physiol (1985). 2020;129(6):1304-9.

7. Munan M, Oliveira CLP, Marcotte-Chénard A, et al. Acute and Chronic Effects of Exercise on Continuous Glucose Monitoring Outcomes in Type 2 Diabetes: A Meta-Analysis. Front Endocrinol (Lausanne). 2020;11:495.

8. Rowell LB. Human cardiovascular adjustments to exercise and thermal stress. Physiological Reviews. 1974;54(1):75-159.

9. Pearson J, Low DA, Stöhr E, et al. Hemodynamic responses to heat stress in the resting and exercising human leg: insight into the effect of temperature on skeletal muscle

blood flow. American Journal of Physiology-Regulatory, Integrative and Comparative Physiology. 2011;300(3):R663-R73.

10. Rowell LB, Brengelmann GL, Blackmon JR, et al. Redistribution of blood flow during sustained high skin temperature in resting man. J Appl Physiol. 1970;28(4):415-20.

11. Detry JM, Brengelmann GL, Rowell LB, et al. Skin and muscle components of forearm blood flow in directly heated resting man. J Appl Physiol. 1972;32(4):506-11.

12. Heinonen I, Brothers RM, Kemppainen J, et al. Local heating, but not indirect whole body heating, increases human skeletal muscle blood flow. Journal of Applied Physiology. 2011;111(3):818-24.

13. Keller DM, Sander M, Stallknecht B, et al. α-Adrenergic vasoconstrictor responsiveness is preserved in the heated human leg. The Journal of Physiology. 2010;588(19):3799-808.

14. Baron AD, Steinberg H, Brechtel G, et al. Skeletal muscle blood flow independently modulates insulin-mediated glucose uptake. Am J Physiol. 1994;266(2 Pt 1):E248-53.

15. Behzadi P, Ravanelli N, Gravel H, et al. Acute effect of passive heat exposure on markers of cardiometabolic function in adults with type 2 diabetes mellitus. J Appl Physiol (1985). 2022;132(5):1154-66.

16. Rivas E, Newmire DE, Crandall CG, et al. An acute bout of whole body passive hyperthermia increases plasma leptin, but does not alter glucose or insulin responses in obese type 2 diabetics and healthy adults. J Therm Biol. 2016;59:26-33.

17. James TJ, Corbett J, Cummings M, et al. Timing of acute passive heating on glucose tolerance and blood pressure in people with type 2 diabetes: a randomized, balanced crossover, control trial. J Appl Physiol (1985). 2021;130(4):1093-105.

18. Su Y, Hoekstra SP, Leicht CA. Hot water immersion is associated with higher thermal comfort than dry passive heating for a similar rise in rectal temperature and plasma interleukin-6 concentration. Eur J Appl Physiol. 2024;124(4):1109-19.

19. Campbell HA, Akerman AP, Kissling LS, et al. Acute physiological and psychophysical responses to different modes of heat stress. Experimental Physiology. 2022;107(5):429-40.

20. Laukkanen JA, Kunutsor SK. The multifaceted benefits of passive heat therapies for extending the healthspan: A comprehensive review with a focus on Finnish sauna. Temperature (Austin). 2024;11(1):27-51.

21. Tsai SR, Hamblin MR. Biological effects and medical applications of infrared radiation. J Photochem Photobiol B. 2017;170:197-207.

22. National Institute of Public Health and the Environment MoH W, and Sport, The Netherlands Dutch Food Composition Database 2021 2021 [Available from: https://www.rivm.nl/en/dutch-food-composition-database.

23. Matsuda M, DeFronzo RA. Insulin sensitivity indices obtained from oral glucose tolerance testing: comparison with the euglycemic insulin clamp. Diabetes Care. 1999;22(9):1462-70.

24. Abdul-Ghani MA, Matsuda M, Balas B, et al. Muscle and Liver Insulin Resistance Indexes Derived From the Oral Glucose Tolerance Test. Diabetes Care. 2007;30(1):89-94.

25. Matthews DR, Hosker JP, Rudenski AS, et al. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia. 1985;28(7):412-9.

26. Hoekstra SP, Bishop NC, Faulkner SH, et al. Acute and chronic effects of hot water immersion on inflammation and metabolism in sedentary, overweight adults. J Appl Physiol (1985). 2018;125(6):2008-18.

27. Faulkner SH, Jackson S, Fatania G, et al. The effect of passive heating on heat shock protein 70 and interleukin-6: A possible treatment tool for metabolic diseases? Temperature (Austin). 2017;4(3):292-304.

28. Maley MJ, Hunt AP, Stewart IB, et al. Hot water immersion acutely reduces peripheral glucose uptake in young healthy males: An exploratory crossover randomized controlled trial. Temperature. 2023:1-10.

29. Hoekstra SP, Ogawa T, Dos Santos M, et al. The effects of local versus systemic passive heating on the acute inflammatory, vascular and glycaemic response. Appl Physiol Nutr Metab. 2021;46(7):808-18.

30. Leicht CA, James LJ, Briscoe JHB, et al. Hot water immersion acutely increases postprandial glucose concentrations. Physiol Rep. 2019;7(20):e14223.

31. Iguchi M, Littmann AE, Chang SH, et al. Heat stress and cardiovascular, hormonal, and heat shock proteins in humans. J Athl Train. 2012;47(2):184-90.

32. Faure C, Charlot K, Henri S, et al. Impaired glucose tolerance after brief heat exposure: a randomized crossover study in healthy young men. Clin Sci (Lond). 2016;130(12):1017-25.

33. Dumke CL, Slivka DR, Cuddy JS, et al. The Effect of Environmental Temperature on Glucose and Insulin After an Oral Glucose Tolerance Test in Healthy Young Men. Wilderness Environ Med. 2015;26(3):335-42.

34. Carroll HA, Templeman I, Chen YC, et al. Effect of acute hypohydration on glycemic regulation in healthy adults: a randomized crossover trial. J Appl Physiol (1985). 2019;126(2):422-30.

35. Akanji AO, Oputa RN. The effect of ambient temperature on glucose tolerance. Diabet Med. 1991;8(10):946-8.

36. Frayn KN, Whyte PL, Benson HA, et al. Changes in forearm blood flow at elevated ambient temperature and their role in the apparent impairment of glucose tolerance. Clin Sci (Lond). 1989;76(3):323-8.

37. Zello GA, Smith JM, Pencharz PB, et al. Development of a heating device for sampling arterialized venous blood from a hand vein. Ann Clin Biochem. 1990;27 (Pt 4):366-72.

38. Hargreaves M, Angus D, Howlett K, et al. Effect of heat stress on glucose kinetics during exercise. J Appl Physiol (1985). 1996;81(4):1594-7.

39. Tatár P, Vigas M, Jurcovicová J, et al. Impaired glucose utilization in man during acute exposure to environmental heat. Endocrinol Exp. 1985;19(4):277-81.

40. Rowell LB, Detry JR, Profant GR, et al. Splanchnic vasoconstriction in hyperthermic man--role of falling blood pressure. J Appl Physiol. 1971;31(6):864-9.

41. Meier JJ, Baller B, Menge BA, et al. Excess glycaemic excursions after an oral glucose tolerance test compared with a mixed meal challenge and self-measured home glucose profiles: is the OGTT a valid predictor of postprandial hyperglycaemia and vice versa? Diabetes Obes Metab. 2009;11(3):213-22.

42. Hesketh K, Shepherd SO, Strauss JA, et al. Passive heat therapy in sedentary humans increases skeletal muscle capillarization and eNOS content but not mitochondrial density or GLUT4 content. Am J Physiol Heart Circ Physiol. 2019;317(1):H114-h23.

43. Pallubinsky H, Phielix E, Dautzenberg B, et al. Passive exposure to heat improves glucose metabolism in overweight humans. Acta Physiol (Oxf). 2020;229(4):e13488.

44. Hooper PL. Hot-tub therapy for type 2 diabetes mellitus. N Engl J Med. 1999;341(12):924-5.

A single sauna session does not improve postprandial blood glucose handling in individuals with type 2 diabetes mellitus: a cross-over, randomized, controlled trial

Running head: Sauna increases postprandial glucose levels

Laura Schenaarts, Floris K Hendriks, Cas J Fuchs, Wendy E Sluijsmans, Tim Snijders, Luc JC van Loon

Department of Human Biology, NUTRIM Institute of Nutrition and Translational Research in Metabolism, Maastricht University, The Netherlands.

Address for correspondence:

Prof. Luc J.C. van Loon

Department of Human Biology

Institute of Nutrition and Translational Research in Metabolism (NUTRIM)

Maastricht University

PO Box 616, 6200 MD Maastricht, The Netherlands

Tel: +(31) 43 3881397

Fax: +(31) 43 3670976

Email: L.vanLoon@maastrichtuniversity.nl