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Hand heating lowers postprandial blood glucose concentrations: A double-blind randomized controlled crossover trial

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ABSTRACT

Objectives: Examine effect of single hand heating with and without negative pressure on fasting blood glucose (FBG) and postprandial blood glucose (PBG).
Design: Double-blind randomized controlled trial with crossover design.
Subjects: FBG experiment: 17 healthy subjects (4 males). PBG experiment: 13 healthy subjects (1 males).
Interventions: Devices included one providing heat only, one heat and negative pressure, and one acting as a sham. For the FBG experiment the devices were used for 30 min. For the PBG experiment the devices were used for one hour during an oral glucose tolerance test (OGTT).
Outcome Measures: Blood glucose measurements were used to determine change in FBG, peak PBG, area under the curve (AUC), and incremental AUC (iAUC).
Results: Temperature: Change in tympanic temperature was ≤ 0.15 °C for all trials. FBG: There was no effect on FBG. PBG: Compared to the sham device the heat plus vacuum and heat only device lowered peak blood glucose by 16(31)mg/dL, p = 0.092 and 18(28)mg/dL, p = 0.039, respectively. AUC and iAUC: Compared to the sham device, the heat plus vacuum device and heat only device lowered the AUC by 5.1(15.0)%, p = 0.234 and 7.9(11.1)%, p = 0.024 respectively and iAUC by 17.2(43.4)%, p = 0.178 and 20.5(34.5)%, p = 0.054, respectively.
Conclusions: Heating a single hand lowers postprandial blood glucose in healthy subjects.

1. Introduction

Humans have used various forms of heat therapy for thousands of years. These ubiquitous practices, including the ancient Roman baths, Japanese hot springs, Finnish saunas, and sweat lodges used by the indigenous people of the Americas, have many health claims associated with them. For example, those reporting 4–7 sauna session per week compared to those reporting 1 sauna session per week were found to have a decreased risk of all-cause mortality, sudden cardiac death, fatal coronary heart disease, fatal cardiovascular disease, Alzheimer's disease, dementia, psychotic disorders, pneumonia and hypertension as well as lower inflammation. [1,2] Other experimental studies have demonstrated improvements in lipid profiles, [3,4] endothelial function, [5,6,7,8] oxidative stress, [9,10] delayed-onset muscle soreness, [11] running performance measured by time to exhaustion, [12] mitochondrial function and atrophy in skeletal muscle during immobilization, [13] premature ventricular contractions in chronic heart failure patients, [14] peripheral artery disease, [15,16] depression, [17,18] heat acclimatization, [19] excretion of heavy metals,[20] sleep quality, [21] inflammation [22], appetite, [23] weight, [23] body fat [23], glycosylated hemoglobin (HbA1c), [24] and fasting glucose.[22,24]

In all of the above forms of heat therapy, the entire body is exposed to heat. Whether partial exposure can elicit similar benefits remains unknown. One therapy using exposure of only a small portion of the body with the potential for improving glycemic control is hand heating. Hand heating at the wrist can increase blood flow which is known to modulate substrate uptake and is positively associated with insulin sensitivity.[25,26] Whether these effects translate to improved glucose tolerance is unknown. Mechanical distension of arteriovenous anastomoses in appendages has also been shown to increase blood flow.[27] By further increasing blood flow, the addition of negative pressure may improve glucose tolerance. If found to be effective, hand heating with or without negative pressure could serve as an adjunct to traditional means of glycemic control such as exercise.

Therefore, the purpose of this study was to examine the effect of heating a single hand with and without negative pressure on blood

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glucose concentrations. One experiment aimed to determine the effect of hand heating with and without negative pressure on fasting blood glucose levels (FBG) while the other investigated the effect on postprandial blood glucose (PBG) in healthy subjects.

2. Methods

2.1. Study design

Both experiments were double-blind, randomized controlled trials which required 3 laboratory visits each to complete. During each visit a different device was used, one providing heat only, one providing both heat and vacuum, and one acting as a sham. All devices appeared and sounded identical. Devices were blinded to both the participant and researcher.

2.2. Participants

Both experiments recruited participants between the ages of 18 and 40 years in apparently good health with no current or past use of diabetes or blood pressure medication. For the FBG experiment, 17 subjects (4 males) were recruited and 13 subjects (1 male) were recruited for the PBG experiment. Subject demographics are shown in Table 1.

The entirety of the experiment was conducted in the Clinical Nutrition and Physiological Sciences Laboratory at San Diego State University. The lab is well-lit, quiet, and maintained at a temperature of 22 °C. Recruitment and data collection occurred from April to August of 2019. All participants provided written informed consent and the study was approved by the Institutional Review Board at San Diego State University.

2.3. Device description

Hand heating was performed on a single hand using the AVACEN 100, a patented and FDA-cleared Class II medical device. The device includes a hard plastic case with a metal plate on the floor of the chamber approximately the size of a human hand. The metal plate is heated to 42 °C and a plastic pneumatic cuff is inflated around the wrist of the inserted hand creating an airtight seal. With the hand and fingers resting on the heated metal plate the air is evacuated from the chamber via a pump creating a vacuum of -30 mmHg. In addition to FDA clearance, a previous clinical study found this device to be well-tolerated with no reported adverse events.[28]

2.4. Interventions

Subjects reported to the laboratory between the hours of 6 a.m. and 10 a.m. following an overnight fast of 8 − 12 h with no restriction on water intake. The subjects were restricted from performing any exercise for 8 − 12 h before each lab visit. Subject visits were scheduled to begin at the same time of day (within 1 h) to minimize circadian related variation. Subjects were also asked to keep the length of their overnight fast consistent (within 1 h) and to maintain their usual diet and lifestyle habits throughout their participation in the study. During each experiment, the subjects blood glucose concentration and tympanic temperature were recorded. Blood glucose was measured using a glucometer (Contour Next) with multiple readings being taken until two values within 5 mg/dL were obtained and subsequently averaged. In order to assess systemic changes, blood glucose was measured in the hand that was not exposed to the intervention. The coefficient of variation for measuring blood glucose was 1.7 %. Tympanic temperature was measured using an infrared ear thermometer (Braun Thermoscan 3).

For the FBG experiment participants used the three devices for 30 min with measurements obtained before and immediately after the 30 min of treatment. For the PBG experiment participants used the three devices during an oral glucose tolerance test. The devices were used for one hour immediately after consuming a 75 g dextrose drink (approximately 12 oz.) and blood glucose levels were followed for two hours. After baseline measurements were obtained subjects consumed the dextrose drink. Time started the moment the subject finished the dextrose drink, which was consumed in less than 5 min in all cases, and measurements were obtained every 30 min thereafter for a total of 2 h.

Table 1
Mean (SD) age and anthropometric variables.

	Age (years)	BMI (kg/m^2)	Weight (kg)	Body Fat (%)
Male (n = 5)	26.5 (3.4)	22.8 (2.0)	72.7 (6.9)	12.0 (3.2)
Female (n = 25)	24.0 (3.5)	23.1 (3.2)	60.9 (8.7)	21.7 (4.7)
Total (N = 30)	24.5 (3.6)	23.0 (3.0)	63.2 (9.5)	19.9 (5.9)

2.5. Statistical analyses

Data are presented as mean (SD) and were analyzed using SPSS version 26. In the FBG experiment, pre-and post-treatment blood glucose values were analyzed using a 2 (time) x 3 (condition) repeated measures ANOVA and paired t-tests were used for the post hoc pairwise comparisons. In the PBG experiment, changes in blood glucose, peak blood glucose, area under the curve (AUC), incremental AUC (iAUC) in the heat plus vacuum and heat only devices relative to the sham device were analyzed using one-way repeated measures ANOVAs and follow up paired t-tests. AUC and iAUC were calculated from the first hour of blood glucose measurements using the trapezium rule and the trapezium rule followed by subtraction of fasting glucose levels, respectively. One-hour glucose is a stronger predictor of future type 2 diabetes risk than 2 -h glucose and is associated with diabetes complications and mortality.[29,30]

Statistical significance was defined as $p \leq 0.05$ and a trend was defined as $p \leq 0.10$.

3. Results

3.1. Tympanic temperature

Change in tympanic temperature was ≤ 0.15 °C for all trials.

Fasting Blood Glucose

There was no omnibus effect for time by trial for fasting blood glucose ($F_{(2,32)} = 2.36$, p = 0.11, $\eta_p^2 = 0.13$). [Fig. 1]

3.2. Peak blood glucose

Following the OGTT the average peak blood glucose occurred at the 30-minute time point as depicted in Fig. 2. There was a significant main effect of condition ($F_{(2,24)} = 3.42$, p = 0.049, $\eta_p^2 = 0.22$). Compared to the sham device the heat plus vacuum and heat only device lowered peak blood glucose by 16 (31) mg/dL, p = 0.092, 95 %CI (-35 to 3 mg/dL) and 18 (28) mg/dL, p = 0.039, 95 %CI (-35 to −1 mg/dL) respectively. There was not a significant difference in peak glucose between the heat plus vacuum and heat only devices, 2 (21) mg/dL, p = 0.732, 95 %CI (-11 to 15 mg/dL)

3.3. AUC and iAUC

There was a trend for main effect for AUC ($F_{(2,24)} = 3.08$, p = 0.065, $\eta_p^2 = 0.20$) and iAUC ($F_{(2,24)} = 2.57$, p = 0.098, $\eta_p^2 = 0.18$) [Figs. 3 and 4]. Pairwise comparisons showed, in relation to the sham device, the heat plus vacuum device and heat only device lowered the AUC by 5.1(15.0)%, 430(1,238)mg·hr/dL, p = 0.234, 95 %CI (-318 to 1,179 mg hr/dL) and 7.9(11.1)%, 671(935)mg·hr/dL, p = 0.024, 95 %CI (106 to 1,236 mg hr/dL) respectively and iAUC by 17.2(43.3)%,

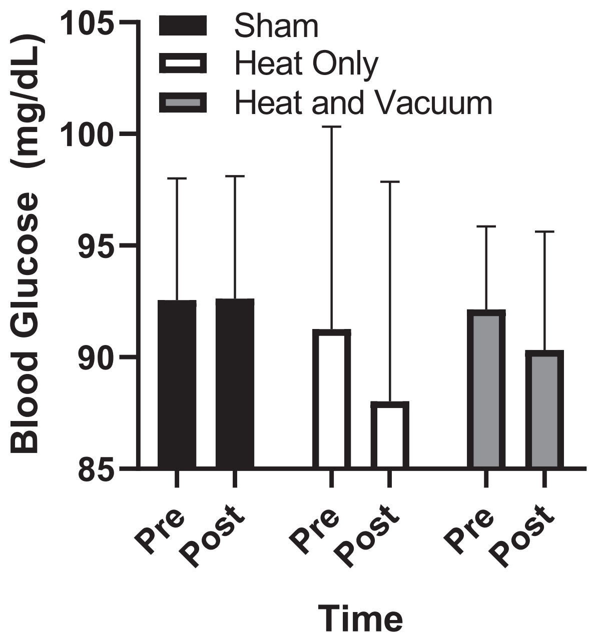

Fig. 1. Mean (SD) blood glucose concentration before and immediately following 30 min of treatment for the 3 conditions. N = 17.
* Indicates statistical significance (p ≤ 0.05)
ˆ Indicates a trend towards statistical significance (p ≤ 0.10)

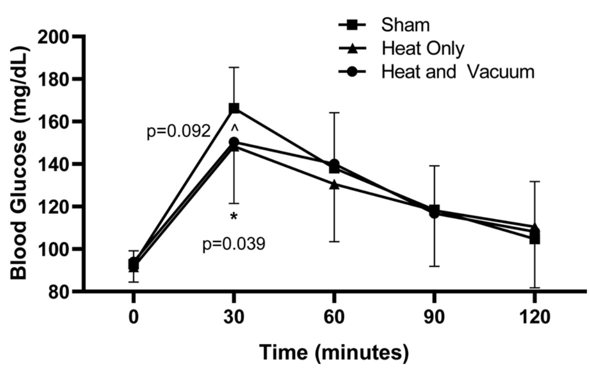

Fig. 2. Mean (SD) blood glucose concentrations before and 120 min following ingestion of 75 g of dextrose for the 3 different conditions. N = 13.

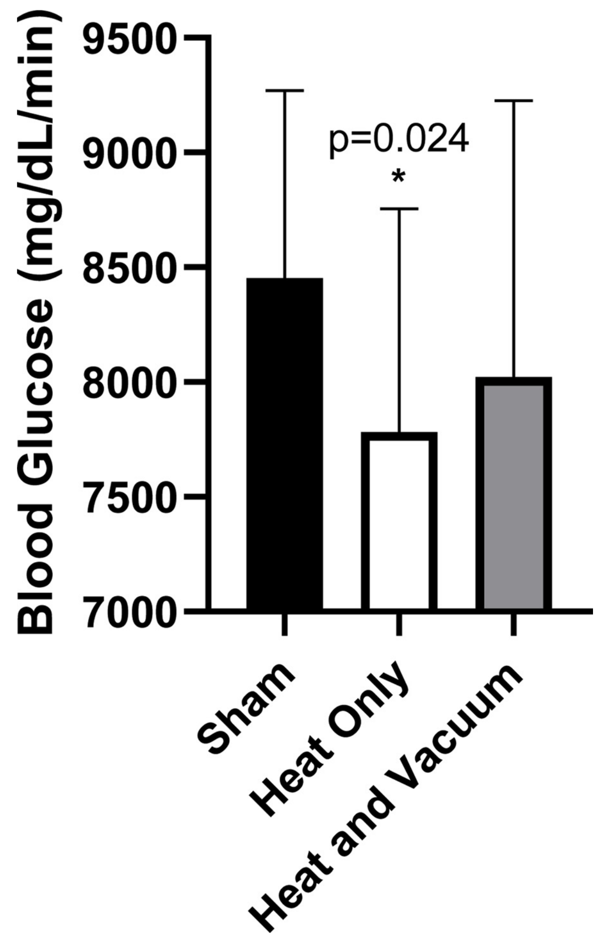

Fig. 3. Mean (SD) 1 h post ingestion area under the curve for the 3 different conditions.
* Indicates statistical significance (p ≤ 0.05)
ˆ Indicates a trend towards statistical significance (p ≤ 0.10)

494(1,247)mg·hr/dL, p = 0.178, 95 %CI (-259 to 1,248 mg hr/dL) and 20.5(34.5)%, 589(994)mg·hr/dL, p = 0.054, 95 %CI (-11 to 1,1190 mg hr/dL) respectively. There was not a significant difference between the heat plus vacuum and heat only devices for AUC (3.0(9.0)%, 240(721)mg·hr/dL, p = 0.252, 95 %CI (-195 to 676 mg hr/dL)) or iAUC (4.0(29.6)%, 95(706) mg·hr/dL, p = 0.637, 95 %CI (-332 to 522 mg hr/dL)).

4. Discussion

This set of experiments was the first to test the effect of hand heating combined with negative hand pressure on fasting and postprandial blood glucose. Although there was no change in fasting blood glucose, there was a significant reduction in the postprandial response following hand heating without negative pressure. Postprandial glycemia is independently associated with risk of various diseases and mortality, often more strongly than fasting glucose or HbA1c.[31–35] This association persists beyond the diagnostic threshold extending its usefulness to diabetics and non-diabetics alike.[36] Targeting postprandial glucose, therefore, appears to be a viable strategy for improving health outcomes. This novel means of attenuating the postprandial response has several advantages over more conventional methods such as exercise. Adherence to exercise is poor with only 23 % of American adults meeting the physical activity guidelines as of 2018.[37] Additionally, some populations, such as those suffering from morbid obesity, osteoarthritis, or spinal injuries may be unable to perform traditional exercise. Considering the non-invasive nature, lack of adverse effects, and ease of use, hand heating devices could potentially serve as an appealing adjunct or alternative to conventional methods of improving glycemic control.

Notably, these results oppose those of whole-body heat exposure. Tatar et al. found that fasting blood glucose levels rose slightly (~13 mg/dL) 10 min into a 30-minute dry sauna session and remained elevated 30 min after completion of said session. Elevations in glucagon, adrenaline, and noradrenaline, but not insulin, were also noted.[38] Kimball et al. observed a 6 mg/dL rise in FBG immediately following heat stress and a return to near baseline 30 min after heat exposure as well as a ~30 mg/dL higher postprandial blood glucose peak and 8 % larger AUC following an OGTT compared to a no heat exposure control condition. The decrease in glucose uptake was seen to a greater extent in non-lean individuals.[39] The same heat exposure protocol was also found to increase norepinephrine.[40]

Differing blood glucose responses to whole-body heat exposure and partial heat exposure may be explained by activation of the sympathetic nervous system during whole-body heat exposure, as evidenced by increases in plasma catecholamines. Catecholamines increase blood glucose, in part, via inhibition of insulin-mediated glycogenesis, increased glycogenolysis, and increased gluconeogenesis.[41] Activation of the

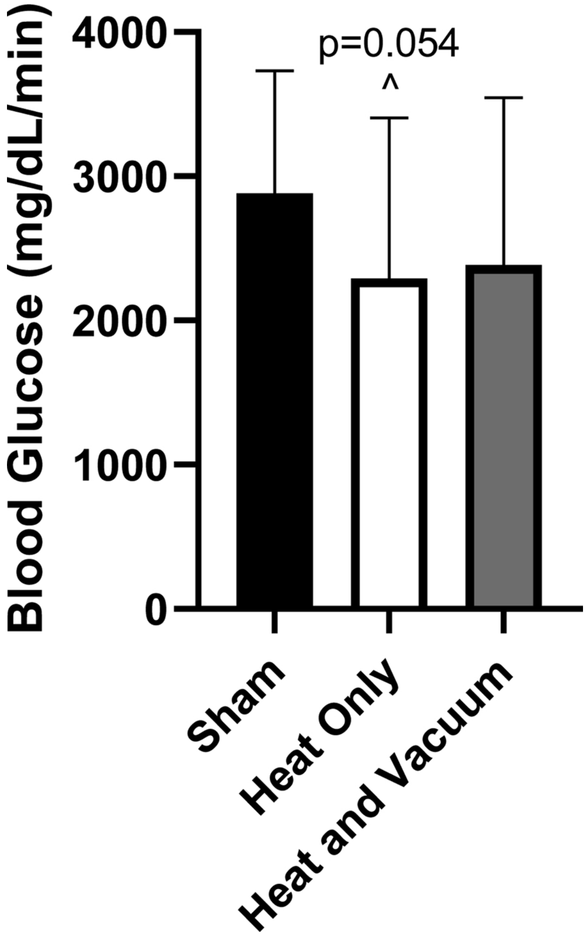

Fig. 4. Mean (SD) 1 h post ingestion integrated area under the curve for the 3 different conditions.
* Indicates statistical significance ($p \leq 0.05$)
ˆ Indicates a trend towards statistical significance ($p \leq 0.10$)

sympathetic nervous system during whole body heat therapy is also supported by changes in heart rate variability (HRV), a biomarker of autonomic nervous system balance. In a cohort of 93 middle-aged men and women with cardiovascular risk factors, but without symptomatic cardiovascular disease, a single 30-minute sauna session resulted in transient changes to several HRV measures suggesting activation of the sympathetic nervous system and/or retraction of the parasympathetic nervous system compared to baseline. After 30 min of post-sauna recovery changes in these measures reversed, suggesting retraction of the sympathetic nervous system and/or activation of the parasympathetic nervous system compared to baseline.[42]

Partial heat exposure via hand heating with negative pressure did not affect tympanic temperature and without an increase in body temperature activation of the sympathetic nervous system as part of a stress response might have been avoided. In the absence of a stress response and subsequent release of catecholamines, the supposed increased blood flow provided by the heat device could be improving glucose tolerance by increasing microvascular recruitment. [43] Glucose regulation is complex and involves multiple organs, hormones and tissues. It is currently unknown what mechanisms are underlying the observed effects and which system(s) are involved.

The decrease in peak blood glucose following hand heating is difficult to put in context but can be compared to other non-pharmaceutical blood glucose lowering interventions. For example, three minutes of postprandial moderate-intensity stairclimbing resulted in a 15 mg/dL reduction compared to a seated control condition.[45] This is similar to the hand heating which resulted in an 18 mg/dL (Fig. 1) decrease. Other non-pharmaceutical interventions with similar PBG reductions include 40 min of postprandial slow-walking which resulted in a 14 mg/dL reduction compared to the seated control condition.[46] Although the many benefits of exercise, including those for blood glucose control and carbohydrate metabolism, are well known, nearly 80 % of Americans fail to meet the physical activity guidelines.[37] Alternative methods of blood glucose control, such as hand heating, may be more appealing to those unwilling or unable to exercise a sufficient amount and therefore could serve as an additional option.

There are several potential limitations of the current experiments. The small sample size may have resulted in underpowered analyses and increased risk of type two error for multiple comparisons that trended towards significance. Participants were predominantly female and though sex differences would not be expected they should not be ruled out. It is possible there was a flooring effect seen with the device on FBG and PBG since all subjects were normoglycemic. Caution may also be warranted with use of this device as one subject in the current study arrived with a FBG of 66 mg/dL and following use of the heat with negative pressure device dropped into the hypoglycemic range with a FBG of 56 mg/dL though without any discomfort. Food intake and physical activity recalls were not performed, however, subjects were asked to maintain their diet and lifestyle habits and any changes should be balanced out from the randomization of conditions. Although the study was designed to be double-blinded, we cannot be sure that subjects were unable to perceive differences in temperature or pressure between devices.

In conclusion, hand heating successfully lowered postprandial blood glucose. Together, the non-invasive nature of the device, magnitude of decrease in postprandial blood glucose, and ease of use highlight the utility of this device.

CRediT authorship contribution statement

Jeff Moore: Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Writing - original draft, Writing - review & editing, Visualization, Project administration. **Jochen Kressler:** Formal analysis, Writing - original draft, Writing - review & editing, Supervision. **Michael J. Buono:** Conceptualization, Methodology, Formal analysis, Resources, Writing - original draft, Writing - review & editing, Supervision, Project administration, Funding acquisition.

Declaration of Competing Interest

The authors declare no conflict of interest. Representatives from AVACEN Medical were not involved in the design implementation, analysis, or interpretation of data from this investigator initiated study.

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