Hand Heating Improves Glucose Tolerance in Individuals with Type 2 Diabetes but not Prediabetes

by

Jeff Moore, B.S./B.S., Jmoore714@gmail.com
Jochen Kressler, PhD, Jkressler@sdsu.edu
Michael Buono, PhD, mbuono@sdsu.edu

School of Exercise and Nutritional Sciences
San Diego State University
San Diego, CA 92182-7251

Running head: Hand heating improves glucose tolerance in T2DM

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Corresponding Author: Jeff Moore
San Diego State University
San Diego, CA 92182-7251

Email: Jmoore714@gmail.com

Phone: (714)-658-7215

Abstract

Background: The prevalence of type 2 diabetes mellitus (T2DM) is increasing worldwide with considerable consequences. Studies have shown heat therapy can improve glycemic measures with a divergence in the effects of whole-body versus partial-body heat therapy. Partial-body heat therapy has been shown to acutely improve glucose tolerance in normoglycemic individuals but its effect in those with impaired glycemic measures is unknown. Methods: In this experiment, the effect of hand heating with (HV) and without (HO) negative pressure on postprandial blood glucose (PBG) compared to a sham device in 20 individuals with elevated fasting blood glucose was examined using a double-blind randomized controlled trial with crossover design. Results: Hand heating had no effect on tympanic temperature ($\Delta T_t \leq 0.1$ °C in all conditions). Among prediabetic individuals, there was no difference in PBG over time, change from baseline to peak PBG, PBG area under the curve (AUC), or PBG incremental area under the curve (iAUC) between any conditions. Among T2DM individuals, there was a main effect for condition for iAUC ($F(2,4) = 36.727$, $p=.003$, $\eta_p^2=.948$) but not PBG over time, change from baseline to peak PBG, or PBG area under the curve (AUC). Reductions in iAUC were found in the HV ((-26(6)%, p=.019, 95%CI(-42 to -10%)) and HO (-11(2)%, p=.014, 95%CI(-16 to -5%)) conditions compared to the sham. HV iAUC was also lower than HO iAUC (-18(7)%, p=.050, 95%CI(-35 to 0%)). Conclusion: Heating one hand lowered PBG in participants with T2DM but not those with prediabetes. Negative pressure increased the reduction in PBG.

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Introduction

Type 2 diabetes mellitus (T2DM) currently constitutes a global crisis. It stands as a leading cause of both death and disability in countries of all income levels, directly costing nearly a trillion dollars to the world.[1] Although it's largely considered a preventable and reversible disease, T2DM continues to increase in prevalence in individuals of all ages.[1,2] The cause is multifactorial and thus it stands to reason that the solution to such a crisis must be as well.

T2DM is characterized by insulin resistance which leads to elevated blood glucose levels. This disease firsts manifests as impaired glucose tolerance, also known as prediabetes.[1,3] The gold standard for assessing glucose tolerance and diabetes status is an oral glucose tolerance test (OGTT). Glucose tolerance is an independent predictor of mortality, heart disease, cardiac events, and diabetes risk, often outperforming other glucose related biomarkers such as fasting glucose or glycosylated hemoglobin (HbA1c).[4-7] The predictive capability of OGTTs is linear and continuous, extending past the diagnostic thresholds and thus offering insight into the risk of disease in populations both with and without impaired glucose tolerance.[8] Conventional treatments, such as medication, diet, and exercise, while effective, can have poor adherence.[9,10] Additional methods of managing this disease can help by serving as either alternatives or adjuncts to these conventional treatments. One such method, heat therapy, appears particularly promising. Heat therapy appears to attenuate the risk of a variety of diseases as well as all-cause mortality.[11-14] However, the effects of heat therapy appear more nuanced in regard to glycemic measures. While the chronic effects of whole-body heat therapy appear beneficial, the acute effects appear

unfavorable with increases in fasting blood glucose and exaggerations of postprandial glycemia.[13-16] The acute impairment of glucose tolerance may be related to increases in core temperature which lead to activation of the sympathetic nervous system (SNS).[15,17,18] Conversely, we have previously shown that partial heat therapy, applied only to one hand, does not lead to increased core temperature and improves acute glycemic control in normoglycemic individuals.[19] In the current study we examine whether heating a single hand, with and without negative pressure, can improve glucose tolerance in those with impaired glycemic measures.

Methods

Study Design

Twenty participants were recruited for this double-blind, randomized, controlled trial with crossover design which consisted of three separate visits. Each visit consisted of a 2-hour OGTT combined with the use of a different device, one providing heat and vacuum (HV), one providing heat only (HO), and one providing neither heat nor negative pressure (sham). The devices all appeared and sounded identical and were blinded to both the participants and researchers.

Participants

Participants between the ages of 18 and 65 years with an elevated fasting glucose (>100mg/dL) were recruited for this experiment. The use of any medications was required to remain consistent throughout participation. Demographics of participants are displayed in Table 1.

Setting

This experiment was conducted in the Clinical Nutrition and Physiological Sciences Laboratory at San Diego State University. The laboratory is quiet, well-lit, and maintained at 22°C. Participant recruitment occurred between April and November of 2019. Participants provided written informed consent and study approval was granted by the Institutional Review Board at San Diego State University.

Device Description

The AVACEN 100, a patented, FDA-cleared Class II medical device, was used for each condition (hand heating with vacuum (HV), hand heating only without vacuum (HO), and sham device with neither heat nor vacuum. This device consists of a metal plate enclosed within an airtight plastic shell and is used by inserting a single hand and resting the palm on the metal plate. During the heated conditions, the metal plate reaches 42 °C whereas during the sham condition it reaches 36 °C. When the vacuum is activated a negative pressure of -30 mmHg is maintained. In past studies this device has proved to be well-tolerated with only one reported potential adverse event, asymptomatic minor hypoglycemia of 56mg/dL following use in a fasted state.

Interventions

Participants visited the laboratory on 3 separate visits between 6 a.m. and 11 a.m. following an overnight fast (8 – 12 h) with ad libitum water consumption. Visits were performed at the same time of day (within 1 h) to minimize potential circadian related variation. Exercise was prohibited for at least 24 h before each visit and visits were required to be at least 48 h no more than 1 week apart. Participants were asked to make no changes to their diet or lifestyle throughout their participation.

During each visit blood glucose and tympanic temperature were measured at baseline and every 30 min after consuming a standard 75g OGTT. Blood glucose measurements were obtained using a glucometer (Contour Next) with multiple readings at each timepoint until two measurements within 5mg/dL were obtained. Readings within 5mg/dL were subsequently average for data analysis. Blood glucose was measured using samples obtained from the hand not using the device in order to capture systemic changes. The glucometer provided blood glucose measurements with a coefficient of variation of 1.7%. Tympanic temperature readings were obtained with an infrared ear thermometer (Braun Thermoscan 3). Participants used each device continuously for 1 h immediately after finishing the OGTT (75g of dextrose dissolved in 12oz. of water). Participants were required to consume their OGTT beverage within 5 min.

Statistical Analyses

Data are displayed as mean (SD) and all analyses were performed using SPSS version 26. Blood glucose was analyzed using a 3 (condition) by 5 (time) repeated measures ANOVA with LSD posthoc comparisons. Changes in peak blood glucose, area under the curve (AUC), and incremental area under the curve (iAUC) were analyzed with one-way repeated measures ANOVAs with LSD posthoc comparisons. AUC was calculated from blood glucose readings over 2 hours using the trapezoidal rule and iAUC was calculated by subtracting baseline blood glucose values from AUC. Further analysis was performed to determine whether glucose responses to treatment were dependent on diabetic status (prediabetic (FBG = 100 to 139 mg/dL) or diabetic (

FBG ≥140 mg/dL)). To this end, FBG was entered as a between-subject factor in all analyses and the sample was stratified by diabetic status.

Results

Tympanic Temperature

Tympanic temperature changed by ≤0.1 °C in all conditions

Blood glucose over time (Figure 1)

There was no main effect for condition ($F(1.387, 26.354) = 1.520$, $p=.235$, $\eta_p^2=.074$) nor was there an interaction between condition and time ($F(5.104, 96.973) = .606$, $p=.669$, $\eta_p^2=.031$). With diabetic status entered as a between-subjects factor there was an interaction between condition, time and diabetic status ($F(4.726, 85.077) = 2.770$, $p=.025$, $\eta_p^2=.133$). Among the prediabetics there was a main effect for time ($F(2.793, 44.681) = 99.284$, $p<.001$, $\eta_p^2=.861$) but not for condition ($F(2, 32) = 1.216$, $p=.310$, $\eta_p^2=.071$) nor was there an interaction between condition and time ($F(4.588, 73.403) = .689$, $p=.621$, $\eta_p^2=.041$). Among the diabetics there was a main effect for time ($F(4, 8) = 45.104$, $p<.001$, $\eta_p^2=.958$) but not for condition ($F(2, 4) = 3.968$, $p=.112$, $\eta_p^2=.665$) nor was there an interaction between condition and time ($F(8, 16) = 1.934$, $p=.124$, $\eta_p^2=.492$).

Change from baseline to peak blood glucose (Figure 2)

There was no main effect for condition ($F(2, 38) = .050$, $p=.951$, $\eta_p^2=.003$). When reanalyzed with the between-subjects factor there was an interaction between condition and diabetic status ($F(2, 36) = 7.869$, $p=.001$, $\eta_p^2=.304$). There was no main effect for condition among the prediabetics ($F(2, 32) = 1.387$, $p = .264$, $\eta_p^2=.080$) but a trend towards significance for the diabetics ($F(2, 4) = 2.770$, $p = .071$, $\eta_p^2=.733$). Pairwise

comparisons revealed HV trended towards being lower than control (-38 (18) mg/dL, p=.066, 95%CI (-82 to 6 mg/dL)) but not compared to HO (-23 (27) mg/dL, p=.278, 95%CI (-90 to -44 mg/dL)) among diabetics.

AUC (Figure 3)

There was no main effect for condition (F(2, 38) = 1.671, p=.210, η_p^2=.081). When reanalyzed with the between-subject factor there was an interaction between condition and diabetic status (F(2, 36) = 20.949, p<.001, η_p^2=.538). Among the prediabetics there was no main effect for condition (F(2,32) = 1.308, p=.284, η_p^2=.076) however there was a trend for a main effect for condition among the diabetics (F(2,4) = 4.965, p=.082, η_p^2=.713).

iAUC (Figure 4)

There was no main effect for condition (F(1.440, 27.362) = .319, p=.658, η_p^2=.017). When reanalyzed with the between-subject factor there was an interaction between condition and diabetic status (F(2, 36) = 16.655, p<.001, η_p^2=.481). Among the prediabetics there was no main effect for condition (F(2,32) = 1.273, p=.294, η_p^2=.074) however there was a main effect for condition among the diabetics (F(2,4) = 36.727, p=.003, η_p^2=.948). Pairwise comparisons revealed HV was lower than control (-26 (6)%, p=.019, 95%CI (-42 to -10%)) and HO (-18 (7)%, p=.050, 95%CI (-35 to 0%)) and HO was lower than control (-11 (2)%, p=.014, 95%CI (-16 to -5%)) among diabetics

Discussion

In this experiment we found that neither the HV nor HO devices reduced the glycemic response in prediabetic participants, however, both devices reduced the glycemic response in type 2 diabetic participants with the HV being more effective than

HO. These results appear to diverge from our previous findings that both HV and HO were equally effective in reducing the postprandial glucose response following in normoglycemic participants.[19]

The lack of an apparent effect in prediabetics could be due to variability caused by the group's diverse glycemic characteristics. While they all had a FBG ≥100mg/dL at the screening visit, some had a FBG <100mg/dL at following visits. Furthermore, in these 17 participants with an elevated FBG between 100 and 125 mg/dL only seven had an elevated PBG ≥140mg/dL at 2 hours in the control condition meaning they had isolated impaired fasting glucose (IFG) with normal glucose tolerance. The other 10 participants with an elevated FBG between 100 and 125 mg/dL had IFG and impaired glucose tolerance (IGT). While both IFG and IGT are insulin resistant states, the site of this insulin resistance differs between these conditions. IFG is characterized predominantly by hepatic insulin resistance, not impaired muscle insulin sensitivity, while IGT is characterized predominantly by muscle insulin resistance rather than impaired hepatic insulin sensitivity.[20] In those with impaired hepatic insulin sensitivity, the benefit to glucose tolerance may be overridden by their exaggerated hepatic glucose output.

The diabetic subjects experienced a pronounced benefit from the HV device. Unlike our previous experiment in which there was no significant difference between the HV and HO device in normoglycemic participants, there was a significant difference between the HV and HO device in participants with diabetes.[19] Microvascular recruitment is an early effect of insulin which regulates glucose uptake in skeletal muscle, however, this is impaired in type 2 diabetes.[21,22] Negative pressure has been

shown to temporarily increase microvascular blood flow in muscle tissue.[23] In these diabetic participants the negative pressure supplied by the HV device may have overcome their disease-induced microvascular impairment by mechanically recruiting the microvasculature and allowing for glucose disposal.

Very few studies have investigated glycemic responses to partial heat exposure as most studies focus on whole-body heat therapy. While whole-body heat therapy tends to have beneficial effects to glycemic measures in the long term, it acutely raises FBG and exaggerates PBG.[13-16] The increase in glycemic measures following whole-body heat therapy is likely due to activation of the sympathetic nervous system (SNS) and subsequent catecholamine release.[15,17,18] These catecholamines increase blood glucose by inhibiting insulin-mediated glycogenesis, increasing glycogenolysis, and increasing gluconeogenesis.[18] By applying heat to only a small portion of the body, and with a tympanic temperature change of ≤0.1 °C in all conditions, this SNS activation and catecholamine release may have been minimized or avoided entirely. As the acute increase in FBG is relatively small compared to the acute increase in PBG and decrease in long term measures like HbA1c following whole body heat therapy, it may be beneficial to reserve the use of whole-body heat therapy for outside of the postprandial state and partial-heat therapy during the postprandial state.

The reduction in PBG in T2DM subjects is likely of clinical significance. PBG is an independent predictor of all-cause mortality, cardiovascular disease and cardiac events.[4-7] Furthermore, the relationship between PBG and disease risk is linear suggesting a consistent reduction in risk with decreases in PBG.[8] While direct comparisons are difficult, the magnitude of reduction following these hand heating

devices is similar, if not larger, than other non-pharmaceutical interventions aimed at lowering postprandial glucose in individuals with type 2 diabetes. Compared to a sedentary control condition, three 15 min bouts of activities of daily living or a single 45 min moderate intensity endurance-type exercise bout reduced cumulative iAUCs from breakfast, lunch, and dinner by 17% and 35% respectively.[24] Pre and post meal resistance exercise reduced 4-hour AUC by 18% and 30% respectively compared to a control condition.[25] There was no difference in 4-hour AUCs with 20 min of pre or post meal walking compared to a rest condition.[26] In this experiment, among the participants with type 2 diabetes, the 2 hour iAUC was 26(6)% (p=.019) and 11(2)% (p=.014) lower after using the HV and HO devices, respectively, compared to the sham device.

We consider this preliminary evidence of the efficacy of partial heat therapy of merit for a few reasons. The magnitude of the reductions in PBG in T2DM subjects were often similar or even greater than those following exercise interventions. Furthermore, although exercise is effective, adherence is often poor.[10] Globally, one in three women and one in four men do not meet the physical activity guidelines.[27] Even worse, individuals with diabetes are less likely to meet physical activity guidelines than their non-diabetic counterparts.[28] Dietary interventions can also be effective for improving glycemic control among individuals with type 2 diabetes but adherence is similarly poor.[10] Lastly certain populations, such as those with spinal cord injuries, morbid obesity, or osteoarthritis, may be unable to perform the exercise interventions shown to be effective. Therefore, partial heat therapy may offer an alternative or adjunctive means of improving glycemic control in those unable or unwilling to make changes to physical activity or dietary habits. Partial heat therapy, like that provided with the device

used in this experiment, could be used after eating. Whether partial heat therapy could be combined with more traditional means of glycemic control, such as medication or exercise, should be explored.

There are several limitations to the current study. The diabetic group is small with only 3 subjects, however, the differences seen between conditions is still notable considering the magnitude of reduction (26(6)%) yielding a large effect size of η_p^2=.948. The diabetic individuals were on average older than those with impaired fasting glucose. Diabetic status was based solely on fasting blood glucose. The postprandial response was measured during an oral glucose tolerance test. Since most people do not consume 75g of glucose without other nutrients that could affect the postprandial response this design lacks ecological validity and serves more as proof of principle. Although the researchers were blinded to the conditions, we cannot be sure that participants could not differentiate between the devices based off sensations from the vacuum or heat. Lastly, the mechanisms behind the attenuation of postprandial glucose need to be confirmed with blood flow, blood viscosity, and nitric oxide potentially playing a role.

Conclusion

Heating a single hand attenuated the glycemic response in participants with T2DM but not those with prediabetes. The addition of negative pressure amplified the reduction in postprandial glycemia.

Acknowledgments

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Author Disclosure Statement

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.

References

1. Roglic G, World Health Organization, eds. *Global Report on Diabetes*. Geneva, Switzerland: World Health Organization; 2016.
2. Hallberg SJ, Gershuni VM, Hazbun TL, Athinarayanan SJ. Reversing Type 2 Diabetes: A Narrative Review of the Evidence. *Nutrients*. 2019;11(4). doi:10.3390/nu11040766
3. Bansal N. Prediabetes diagnosis and treatment: A review. *World J Diabetes*. 2015;6(2):296-303. doi:10.4239/wjd.v6.i2.296
4. Cavalot F, Pagliarino A, Valle M, et al. Postprandial Blood Glucose Predicts Cardiovascular Events and All-Cause Mortality in Type 2 Diabetes in a 14-Year Follow-Up: Lessons from the San Luigi Gonzaga Diabetes Study. *Diabetes Care*. 2011;34(10):2237-2243. doi:10.2337/dc10-2414
5. Lind M, Tuomilehto J, Uusitupa M, et al. The Association between HbA1c, Fasting Glucose, 1-Hour Glucose and 2-Hour Glucose during an Oral Glucose Tolerance Test and Cardiovascular Disease in Individuals with Elevated Risk for Diabetes. *PLOS ONE*. 2014;9(10):e109506. doi:10.1371/journal.pone.0109506
6. Abdul-Ghani MA, Lyssenko V, Tuomi T, et al. Fasting Versus Postload Plasma Glucose Concentration and the Risk for Future Type 2 Diabetes: Results from the Botnia Study. *Diabetes Care*. 2009;32(2):281-286. doi:10.2337/dc08-1264
7. Zhu J, Xing G, Shen T, et al. Postprandial Glucose Levels Are Better Associated with the Risk Factors for Diabetes Compared to Fasting Glucose and Glycosylated Hemoglobin (HbA1c) Levels in Elderly Prediabetics: Beneficial Effects of Polyherbal Supplements—A Randomized, Double-Blind, Placebo Controlled Trial. Evidence-Based Complementary and Alternative Medicine. doi:https://doi.org/10.1155/2019/7923732
8. Levitan EB, Song Y, Ford ES, et al. Is Nondiabetic Hyperglycemia a Risk Factor for Cardiovascular Disease?: A Meta-analysis of Prospective Studies. *Arch Intern Med*. 2004;164(19):2147-2155. doi:10.1001/archinte.164.19.2147
9. 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;10:1299-1307. doi:10.2147/PPA.S106821
10. Klinovszky A, Kiss IM, Papp-Zipernovszky O, et al. Associations of different adherences in patients with type 2 diabetes mellitus. *Patient Prefer Adherence*. 2019;13:395-407. doi:10.2147/PPA.S187080
11. Laukkanen T, Kunutsor SK, Zaccardi F, et al. Acute effects of sauna bathing on cardiovascular function. *Journal of Human Hypertension*. 2018;32(2):129-138. doi:10.1038/s41371-017-0008-z
12. Laukkanen JA, Laukkanen T, Kunutsor SK. Cardiovascular and Other Health Benefits of Sauna Bathing: A Review of the Evidence. *Mayo Clinic Proceedings*. 2018;93(8):1111-1121. doi:10.1016/j.mayocp.2018.04.008
13. Hoekstra SP, Bishop NC, Faulkner SH, et al. Acute and chronic effects of hot water immersion on inflammation and metabolism in sedentary, overweight adults. *Journal of Applied Physiology*. 2018;125(6):2008-2018. doi:10.1152/japplphysiol.00407.2018

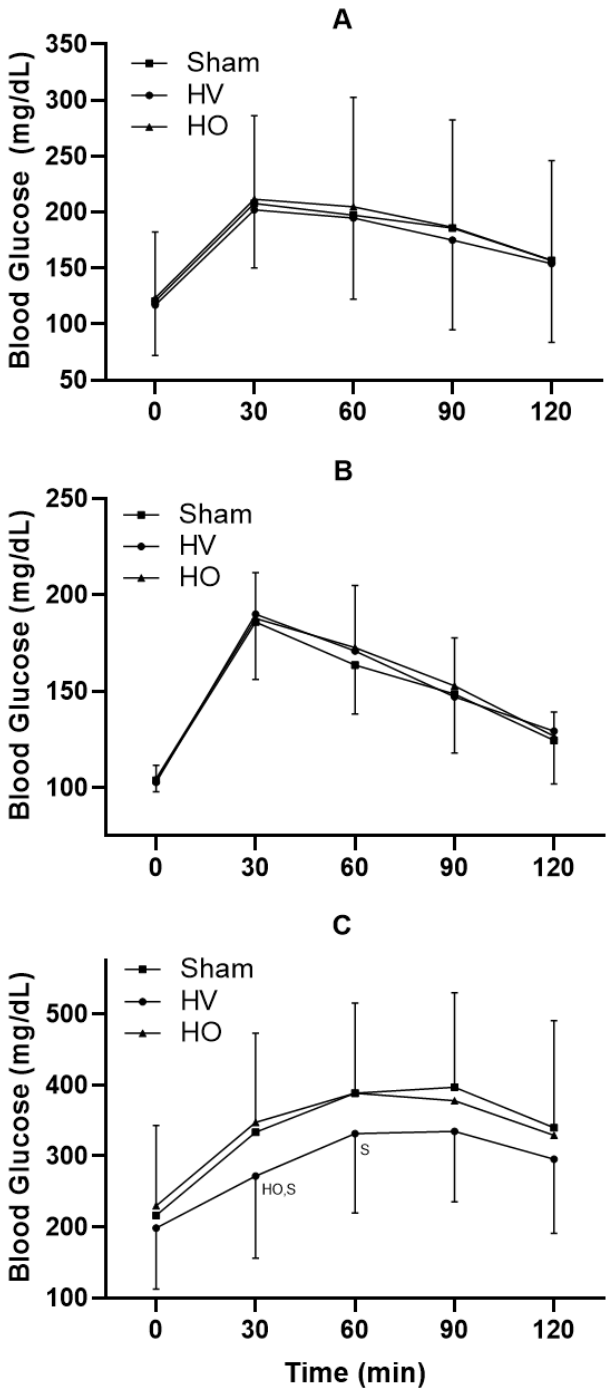
14. Hooper PL. Hot-Tub Therapy for Type 2 Diabetes Mellitus. *New England Journal of Medicine*. 1999;341(12):924-925. doi:10.1056/NEJM199909163411216
15. Tatár P, Vigas M, Jurcovicová J, et al. Increased glucagon secretion during hyperthermia in a sauna. *Eur J Appl Physiol Occup Physiol*. 1986;55(3):315-317. doi:10.1007/bf02343805
16. Kimball AL, McCue PM, Petrie MA, et al. Whole body heat exposure modulates acute glucose metabolism. *International Journal of Hyperthermia*. 2018;35(1):644-651. doi:10.1080/02656736.2018.1516303
17. Iguchi M, Littmann AE, Chang S-H, et al. Heat Stress and Cardiovascular, Hormonal, and Heat Shock Proteins in Humans. *Journal of Athletic Training*. 2012;47(2):184-190. doi:10.4085/1062-6050-47.2.184
18. Barth E, Albuszies G, Baumgart K, et al. Glucose metabolism and catecholamines. *Read Online: Critical Care Medicine | Society of Critical Care Medicine*. 2007;35(9):S508. doi:10.1097/01.CCM.0000278047.06965.20
19. Moore J, Kressler J, Buono MJ. Hand heating lowers postprandial blood glucose concentrations: A double-blind randomized controlled crossover trial. *Complementary Therapies in Medicine*. 2020;49:102280. doi:10.1016/j.ctim.2019.102280
20. Abdul-Ghani MA, Tripathy D, DeFronzo RA. Contributions of β-Cell Dysfunction and Insulin Resistance to the Pathogenesis of Impaired Glucose Tolerance and Impaired Fasting Glucose. *Diabetes Care*. 2006;29(5):1130-1139. doi:10.2337/dc05-2179
21. Vincent MA, Clerk LH, Lindner JR, et al. Microvascular Recruitment Is an Early Insulin Effect That Regulates Skeletal Muscle Glucose Uptake In Vivo. *Diabetes*. 2004;53(6):1418-1423. doi:10.2337/diabetes.53.6.1418
22. Keske MA, Dwyer RM, Russell RD, et al. Regulation of microvascular flow and metabolism: An overview. *Clinical and Experimental Pharmacology and Physiology*. 2017;44(1):143-149. doi:10.1111/1440-1681.12688
23. Borgquist O, Ingemansson R, Malmsjö M. Wound Edge Microvascular Blood Flow during Negative-Pressure Wound Therapy: Examining the Effects of Pressures from –10 to –175 mmHg. *Plastic and Reconstructive Surgery*. 2010;125(2):502-509. doi:10.1097/PRS.0b013e3181c82e1f
24. Dijk J-W van, Venema M, Mechelen W van, et al. Effect of Moderate-Intensity Exercise Versus Activities of Daily Living on 24-Hour Blood Glucose Homeostasis in Male Patients With Type 2 Diabetes. *Diabetes Care*. 2013;36(11):3448-3453. doi:10.2337/dc12-2620
25. Heden TD, Winn NC, Mari A, et al. Postdinner resistance exercise improves postprandial risk factors more effectively than predinner resistance exercise in patients with type 2 diabetes. *Journal of Applied Physiology*. 2014;118(5):624-634. doi:10.1152/japplphysiol.00917.2014
26. Colberg SR, Zarrabi L, Bennington L, et al. Postprandial Walking is Better for Lowering the Glycemic Effect of Dinner than Pre-Dinner Exercise in Type 2 Diabetic Individuals. *Journal of the American Medical Directors Association*. 2009;10(6):394-397. doi:10.1016/j.jamda.2009.03.015
27. Guthold R, Stevens GA, Riley LM, et al. Worldwide trends in insufficient physical activity from 2001 to 2016: a pooled analysis of 358 population-based surveys

with 1·9 million participants. *The Lancet Global Health*. 2018;6(10):e1077-e1086. doi:10.1016/S2214-109X(18)30357-7

Table 1

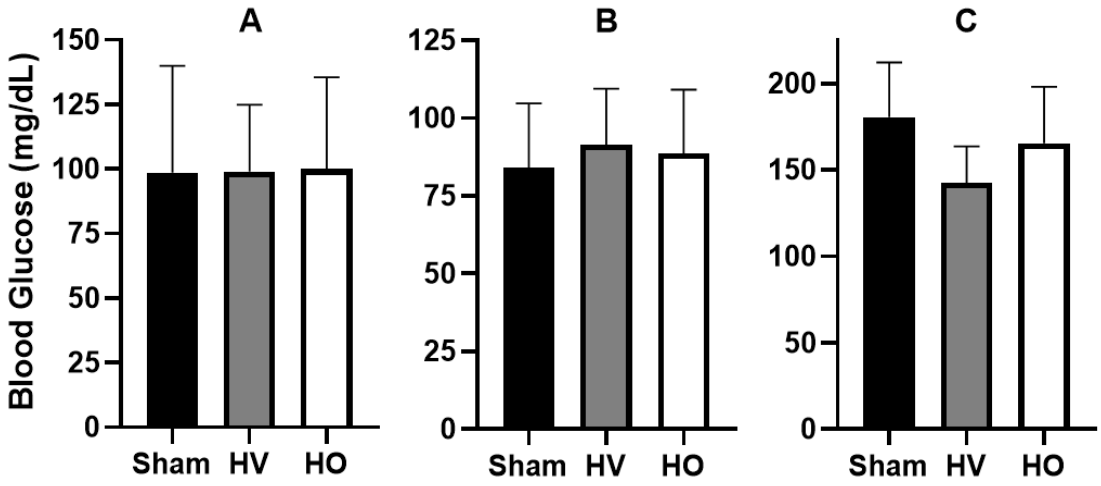
	Age (y)	BMI (kg/m^2)	Weight (kg)	Fasting Glucose (mg/dL)
All (N=20)	30.3 (14.3)	31.8 (5.0)	94.9 (16.1)	124 (53)
Prediabetic (n=17)	26.5 (10.5)	31.6 (5.1)	94.2 (17.1)	106 (6)
Diabetic (n=3)	51.7 (16.2)	32.8 (5.0)	98.9 (8.7)	221 (97)

Figure 1



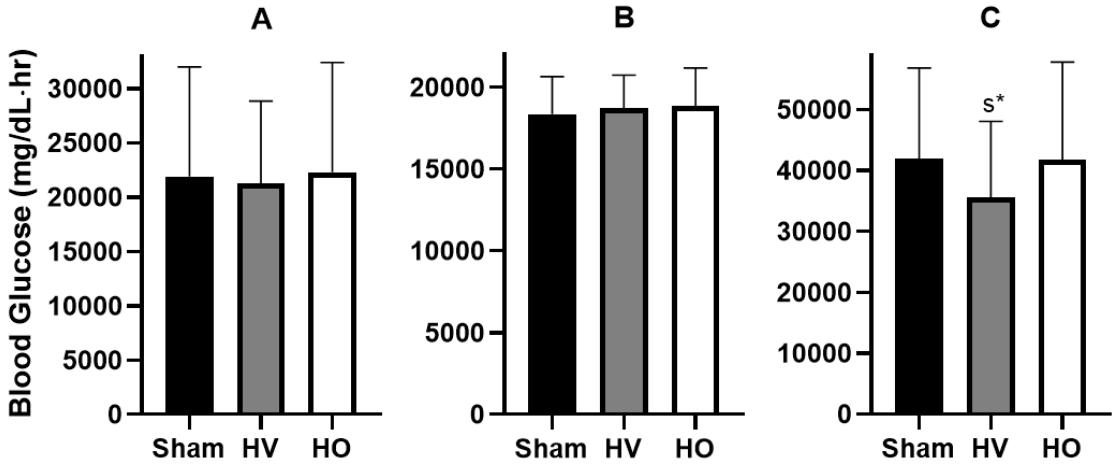
Blood glucose over time for A) all subjects (N=20) , B) prediabetics (n=17), and C) diabetics (n=3)
S indicates difference from sham ($p \leq .05$)
HO indicates difference from HO ($p \leq .05$)

Figure 2



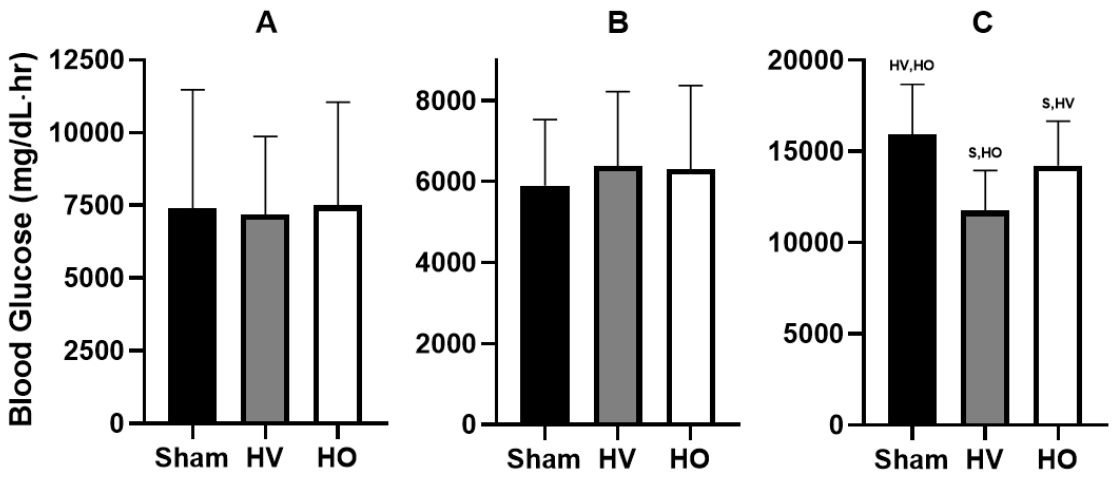
Difference between peak blood glucose and baseline blood glucose for A) all subjects (N=20) , B) prediabetics (n=17), and C) diabetics (n=3)

Figure 3



AUC for A) all subjects (N=20) , B) prediabetics (n=17), and C) diabetics (n=3)
S* indicates trend for difference from sham (p≤.10)

Figure 4



iAUC for A) all subjects (N=20) , B) prediabetics (n=17), and C) diabetics (n=3)
S indicates difference from sham (p≤.05)
HV indicates difference from HV (p≤.05)
HO indicates difference from HO (p≤.05)