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Obese type 2 diabetics have a blunted hypotensive response to acute hyperthermia therapy that does not affect the perception of thermal stress or physiological strain compared to healthy adults

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HIGHLIGHTS

- Hyperthermia therapy may be a novel alternative to improve cardiovascular and metabolic control in obese type 2 diabetics.
- However, diabetics may have an increased risk for heat-related illness due to altered autonomic function and neuropathy caused by uncontrolled hyperglycemia.
- This study found an acute bout of hyperthermia treatment robustly reduced mean arterial blood pressure, but the diabetics had attenuated hyperthermia-hypotension response compared to healthy controls.
- The differences in blood pressure did not affect the physiological strain index or thermal sensation in obesity type 2 diabetics.
- In this study group, whole body hot water immersion may provide a safe alternative for improving cardiovascular health.

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ABSTRACT

Purpose: The objective of this study was to test the hypothesis that a hyperthermia-hypotensive challenge via whole body hot water immersion would alter the perception of hyperthermia and physiological strain in obese type 2 diabetics (T2DM) compared to healthy non-obese (HC) individuals. Additionally, we hypothesize that the mechanisms would be attributed to impaired blood pressure adjustments and afferent signals (via changes in internal and mean skin temperatures).
Methods: In random order, eleven obese T2DM (50 ± 12 y, 45 ± 7% fat mass, 7.5 ± 1.8% HbA1c) and nine similar aged (41 ± 14 y, $P > 0.05$) HC non-obese (33 ± 8% fat mass, $P < 0.01$) non-diabetic (5.3 ± 0.4% HbA1c, $P < 0.01$) underwent a 60 min bout of whole body passive hyperthermia followed by 60 min of recovery or a 2 h resting control condition. The perception of thermal sensation (TS, scale range: 1–13), calculated physiological strain (PSI), internal (T_{re}, rectal) and mean skin (T_{sk}) temperatures, heart rate (HR) and blood pressures (BP) were the primary dependent variables.
Results: Hyperthermia similarly increased T_{re} by 1.4 ± 0.4 °C, T_{sk} by 6.5 ± 0.8 °C and HR by 34 ± 8 bpm in both groups ($P > 0.5$). Hyperthermia reduced diastolic BP (27% in T2DM and 33% in HC, $P < 0.05$) and mean arterial BP (reduced by 15% in T2DM and by 19% in HC) relative to control conditions ($P < 0.05$). The reduction of mean arterial BP area under the curve was attenuated in T2DM (12%) compared to HC (30%) (group × condition, $P < 0.01$). TS and PSI during hyperthermia were not different between groups. Pearson product correlation reported strong correlations ($r = 0.69$–0.89) with T_{re} and T_{sk} with TS in both populations. The linear stepwise regression analysis revealed similar relative contributions for T_{re} (~60%) and T_{sk} (~40%) on TS for both groups.
Conclusions: These data indicate that obese T2DM with moderate metabolic control have an attenuated hyperthermia-hypotensive response that does not affect TS and PSI. This also may suggest behavioral thermoregulation is intact in this study group.

1. Introduction

Type 2 diabetes mellitus (T2DM) is associated with insulin resistance and impaired pancreatic β-cell function, which negatively influences blood glucose homeostasis. Moreover, uncontrolled hyperglycemia will cause microvascular and macrovascular complications that will damage

Abbreviations: AUC, incremental area under the curve; BP, blood pressure; BSA, body surface area; B_t, mean body temperature; HC, healthy control non-obese; HR, heart rate; PSI, physiological strain index; T2DM, diabetes mellitus type 2; T_{re}, internal rectal temperature; T_{sk}, mean skin temperature; TS, thermal sensation.

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and impair vascular function [1,2]. Thus, diabetes increases the risk for heart attack, stroke, end-stage renal disease and blindness [3]. While exercise is beneficial [4,5], diabetics have very low exercise capacities [6,7]. Interestingly, passive hyperthermia treatments may offer benefits comparable to exercise and may provide a novel alternative approach to improve the damaging conditions from diabetes [8]. Repeated heat stress improves vascular endothelial function [9,10], mitochondrial biogenesis [11] and myocardial function [12,13]. Most importantly, a few human studies have also reported that acute and chronic passive hyperthermia therapy (via hot bath immersion and sauna) can improve endothelial function, reduce body weight and blood pressure, and alter hormonal responses in obese, hypertensive, chronic heart failure and diabetic patients [14–18].

However, exposing an individual to a hyperthermic condition can increase the risk for heat-related injuries and/or death. For example, epidemiological data suggest that during record setting heat waves, the risk of heat-related death is increased in people with known medical problems [19,20]. These data report that during heat waves hospitalization and emergency department visits increase in patients with diagnosed diabetes, electrolyte imbalance, and cardiovascular diseases [21–23]. Moreover, obese individuals are at an increased risk for heat illness [24,25] possibly due to the storage of more heat compared to non-obese individuals while performing physical activity in hot conditions [26].

The skin, being an important organ for maintaining thermoregulation, alters cutaneous blood flow [27,28], and perceives heat stress via thermoreceptors [29]. Notably, patients with diabetes have impaired nocturnal thermoregulation and sensory nerve abnormalities that are correlated with fasting blood glucose and hemoglobin A1c levels [30–32]. Therefore, the ability to sense the extent of the heat stress prior to dangerous elevations in body temperature is an important behavior thermoregulatory mechanism that assists in preventing heat-related injury [33] that may be compromised in people with diabetes.

Additionally, hyperthermia increases the risk for a hypotensive-syncope response during and post whole body hyperthermia via hot tub immersion. One study reported the dangers of a 20 min immersed at 41 °C and found hypotensive responses in which 3 healthy men reached near syncope [34]. However, others reported safe hemodynamic responses for coronary artery disease patients in 40 °C [35] and in hypertensive adults it was suggested to be beneficial for reducing blood pressure during a 10 min immersion [16]. No studies have examined if obese T2DM have altered thermal perception or impaired cardiovascular adjustments to whole body hot water immersion. If diabetics have an impaired perception to heat coupled with diminished vascular function, then a compromised cardiovascular response from heat gained and/or perception to dangerous elevations in body temperature in a hot environment may increase the risk for heat-related illness or death. Given the cardiovascular benefits of hyperthermia therapy reported by others [9,10,12–18], understanding the acute thermal stress response via hot water immersion on the cardiovascular system and perception provide important safety implications in populations at risk for cardiovascular disease.

Therefore, our objective was to test the hypothesis that a hyperthermia-hypotensive challenge via whole body hot water immersion would alter the perception of hyperthermia in obese T2DM compared to healthy individuals and the mechanisms would be attributed to impaired blood pressure adjustments and afferent signals (via changes in internal and mean skin temperatures).

2. Material and methods

2.1. Experimental study design

The experimental design was a repeated measures design across two conditions. The initial prescreening consisted of obtaining a written consent, health and physical activity questionnaire, measures of body composition, height, weight, and waist circumference, which then followed a familiarization of all experimental procedures. Prior to testing, a 10–12 h fasting blood plasma sample followed by a standard 2 h 75 g oral glucose tolerance test was administered for glucose (Yellow Springs Instruments Model 2300 Stat Plus Analyzer), and insulin (MAGPIX, Luminex xMAP technology, Millipore, Billerica, MA, USA). Blood samples were placed in sterile blood collection tubes (EDTA) and centrifuged at 4 °C at 3000 rpm for 10 min. Fasting samples were analyzed for hemoglobin A1c and a lipid panel at a clinical laboratory at Texas Health Presbyterian hospital in Dallas TX to determine the severity of diabetes and metabolic syndrome. Body composition was measured using Dual-energy X-ray absorptiometry (DXA, General Electric, Lunar Prodigy Promo, Madison, WI). Following familiarization, all participants were randomized (coin flip) for the completion of two conditions: 1) control-thermoneutral rest; and 2) hyperthermia via hot water immersion. Subjects were asked to record and replicate a three-day dietary food log prior to each visit. All subjects visited the laboratory between 700 and 800 h after an overnight 8–10 h fast. After instrumentation, subjects rested in a seated position for 30 min at ambient room temperatures of ~24 °C and ~58% humidity. During baseline and recovery from hyperthermia, no differences ($P > 0.05$) in environmental temperatures were observed (T2DM 24.1 ± 1.4 °C; HC 23.2 ± 0.6 °C; T2DM 56 ± 0.1%; HC 57 ± 0.1%). Pre-heating baseline measures were taken after 30 min of rest. Subjects were then placed in a sling and winch lifted into a water tank and immersed to the clavicle with water temperature set at ~39 °C with no differences ($P > 0.05$) between group treatments (T2DM 39.4 ± 0.3; HC 39.3 ± 0.4 °C). Subjects rested in this water for 1 h, while internal (rectal), mean skin temperatures, heart rate, blood pressure, and thermal perceptions were recorded every 10 min. Following the 1 h water immersion, the participants were raised and then lowered out of the water and rested in seated position for 1 h. Immediately post immersion, a towel was given to dry off water and a pre-measured 500 mL bottle of water was provided for ad libitum drinking. The remaining water was measured again at end of trial.

2.2. Participants

Eleven obese T2DM and nine HC non-obese inactive men and women were recruited for this study. Subjects were not heat acclimated prior to testing (Table 1). The type 2 diabetes classification was based on the American Diabetes Association recommendation (fasting plasma glucose > 126 mg/dL, HbA1C > 6.5% and a 2 h 75 g glucose tolerance test of >199 at the 2 h time point) [36]. Our data on glycemic control

Table 1
Subject characteristics (mean ± SD).

	T2DM	HC
Number of subjects (male/female)	11 (3/8)	9 (2/7)
Age (y)	50.1 ± 12	41.1 ± 14
Anthropometric		
Weight (kg)	112.0 ± 27*	74.0 ± 12
Height (cm)	167 ± 10	169 ± 9
Waist circumference (cm)	119.6 ± 11	89.0 ± 10
Fat mass (kg)	55.7 ± 25*	25.7 ± 9
Fat mass (%)	45.7 ± 7*	34.6 ± 8
Lean mass (kg)	65.8 ± 20	54.5 ± 23
BSA (m^2)	2.2 ± 0.29*	1.8 ± 0.17
BMI ($kg \cdot m^2$)	40.2 ± 7*	26.4 ± 4
Metabolic		
HbA1c (%)	7.5 ± 1.7*	5.3 ± 0.3
Fasting plasma glucose (mg/dL)	151.1 ± 50*	90.6 ± 10
Fasting plasma insulin (uU/mL)	15.9 ± 6*	6.5 ± 3
2 h OGTT (mg/dL)	266.3 ± 93*	99.5 ± 34
HDL	36.4 ± 7*	58.3 ± 12
LDL	120.1 ± 49*	91.7 ± 14
Cholesterol	192.6 ± 55	168.4 ± 21
Triglyceride	168.4 ± 22*	73.6 ± 43

BMI, body mass index; BSA, Body surface area; HbA1c, Hemoglobin A1c; OGTT, Oral glucose tolerance test; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
* Statistically different from healthy control ($P < 0.05$).