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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

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ABSTRACT

Acute and chronic hyperthermic treatments in diabetic animal models repeatedly improve insulin sensitivity and glycemic control. Therefore, the purpose of this study was to test the hypothesis that an acute 1 h bout of hyperthermic treatment improves glucose, insulin, and leptin responses to an oral glucose challenge (OGTT) in obese type 2 diabetics and healthy humans. Nine obese (45 ± 7.1% fat mass) type 2 diabetics (T2DM: 50.1 ± 12y, 7.5 ± 1.8% HbA1c) absent of insulin therapy and nine similar aged (41.1 ± 13.7y) healthy non-obese controls (HC: 33.4 ± 7.8% fat mass, $P < 0.01$; 5.3 ± 0.4% HbA1c, $P < 0.01$) participated. Using a randomized design, subjects underwent either a whole body passive hyperthermia treatment via head-out hot water immersion (1 h resting in 39.4 ± 0.4 °C water) that increased internal temperature above baseline by $\Delta 1.6 \pm 0.4$ °C or a control resting condition. Twenty-four hours post treatments, a 75 g OGTT was administered to evaluate changes in plasma glucose, insulin, C-peptide, and leptin concentrations. Hyperthermia itself did not alter area under the curve for plasma glucose, insulin, or C-peptide during the OGTT in either group. Fasting absolute and normalized (kg · fat mass) plasma leptin was significantly increased ($P < 0.01$) only after the hyperthermic exposure by 17% in T2DM and 24% in HC groups ($P < 0.001$) when compared to the control condition. These data indicate that an acute hyperthermic treatment does not improve glucose tolerance 24 h post treatment in moderate metabolic controlled obese T2DM or HC individuals.

1. Introduction

Diabetes mellitus (T2DM) is a complex and heterogeneous disease that causes multi-organ dysfunction that affects 25.8 million people (8.3% of the U.S. population) (American Diabetes Association, 2014). Type 2 diabetes (T2DM) presents a low-grade inflammatory state, coupled with lipotoxicity, that impairs the normal insulin cell signaling in various organs (Schaffer, 2003). These impairments, cause peripheral and hepatic insulin resistance and impaired pancreatic β-cell function, which negatively influences blood glucose homeostasis. Additionally, uncontrolled hyperglycemia will damage the micro- and macrovascular, leading to atherosclerosis and hypertension that contribute to stroke and cardiovascular disease. Therefore, treatments that improve glycemic control such as medication, exercise, and diet are important for controlling glycemia and reducing the complications and comorbidities associated with diabetes.

It is well established that chronic exercise can improve blood glucose, lipid, and blood pressure profiles, which prevent or delay chronic complications of diabetes (American Diabetes Association, 2014). Additionally, an acute bout of aerobic exercise can improve whole body insulin sensitivity up to 12–24 h post exercise (Hawley and Lessard, 2008; Wojtaszewski et al., 2000) by insulin independent mechanisms. Moreover, a byproduct of muscle contraction during exercise is heat production, which can increase muscle temperature up to 44 °C (Brooks et al., 1971). Exercise also enhances blood flow, which contributes to the delivery and disposal of insulin and glucose to insulin sensitive tissues.

Abbreviations: T2DM, diabetes mellitus type 2; HC, healthy control; iAUC, incremental area under the curve; OGTT, 75 g oral glucose tolerance test

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Importantly, diabetes causes impaired resting (Johnstone et al., 1993) and exercise leg blood flow (Kingwell et al., 2003). In this context, passive hyperthermia may offer similar benefits comparable to exercise such as increasing blood flow (Song, 1984) and improving glucose uptake and insulin signaling (Gupte et al., 2011).

Recent studies on obesity-induced insulin resistance support a complex inter-regulatory relationship between low intracellular heat shock protein (HSP), increased inflammation (i.e., C-Jun terminal kinase, JNK) and serine hyper-phosphorylation on the insulin receptor substrate (IRS) that impaires insulin signaling (Chung et al., 2008; Gupte et al., 2009; Gupte et al., 2011). Notably, a reversal of these impairments are found after acute and chronic passive hyperthermic treatments. Enhanced insulin signaling are attributed to a reducing inflammation, by increasing intracellular HSPs while improving glycemic control (Chung et al., 2008; Gupte et al., 2011; Kavanagh et al., 2011; Kondo et al., 2012). The independent effect of increasing HSP are shown by drug induced interventions (Vigh et al., 2007), exercise (Quindry, 2012; Whitham and Fortes, 2008), and passive hyperthermia (Chung et al., 2008; Gupte et al., 2009; Gupte et al., 2011) with each reporting improvements on insulin sensitivity and glucose uptake in diabetes-induced animal models. Most importantly, one bout of heat treatment in rats improved insulin-stimulated glucose uptake in skeletal muscle in vivo as well as in vitro (Gupte et al., 2011), but the effect on humans remains untested.

To date, only one preliminary report has investigated the effects of heat "therapy" at rest (via hot-tub immersion) in type 2 diabetics (Hooper, 1999). Following three weeks of hot tub immersion for 30 min a day for 6 days a week, reductions in mean fasting plasma glucose levels (10.1 ± 2.0–8.8 ± 2.3 mmol L^{-1}) coupled with a significant reduction (from $11.3 \pm 3.1\%$ to $10.3 \pm 2.6\%$) in hemoglobin A1c (HbA1c) values were reported. Although they did not asses glycemic control using an oral glucose challenge or evaluate satiety hormonal changes, they reported a trend for reduced body mass ($P=0.08$), which may suggest secondary effects from the chronic heat stress on metabolic control. If this is the case, a major satiety hormone such as leptin, which is a long-term regulator of energy balance will suppress food intake. If caloric intake is reduced by hyperthermia increasing leptin, this may support the concept of reducing adiposity and thereby improve glycemic control (Klok et al., 2007; Ross, 2003; Ryan et al., 2014) under chronic repeated bouts of hyperthermia. Despite a number of animal studies demonstrating beneficial effects of heat therapy on glycemic control and insulin sensitivity, no other human trials in a diabetic population have investigated the influence of an acute bout of passive heat stress in obese type 2 diabetics. Therefore, the aim of this study was to investigate an acute bout of hyperthermia via whole body hot water immersion on insulin, C-peptide, glucose, and leptin response to a glucose challenge.

2. Material and methods

2.1. Participants

Nine (3/6F; 50.1 ± 12y) sedentary obese type 2 diabetic (T2DM) and nine (2/7F; 41.1 ± 13.7y) healthy non-obese sedentary controls (HC) were recruited for this study (see Table 1). Subjects were not heat acclimated prior to testing. The type 2 diabetes classification was based on the American Diabetes Association recommendation (fasting plasma glucose >7.0 mmol L^{-1}, HbA1C $>6.5\%$ and a 2 h 75 g glucose tolerance test of >11.1 mmol L^{-1}) (American Diabetes Association, 2014). Obesity was defined by published guidelines with $>39\%$ body fat considered obese (Gallagher et al., 2000). Subjects were excluded if they had impaired cardiac, neurological, or renal function, were on insulin therapy, smokers or were classified as Type 1 diabetic. Females were tested during the early follicular phase to control for their menstrual cycle. Only two females within the group were post-menopausal (one in each T2DM and HC group). An initial prescreening consisted of obtaining written consent, health and physical activity questionnaires, and measures of body composition (DXA, General Electric, Lunar Prodigy Promo, Madison, WI), weight (Tanita, Arlington Heights, IL), height, and waist circumference (standard scales). Following the initial screening, subjects were familiarized with all experimental procedures. All subjects were physically inactive, defined as not participating in an organized exercise program or exercising more than two days/week of >30 min of moderate to vigorous exercise. Subjects were asked to refrain from any physical exercise and alcohol consumption three days prior to each visit. Subjects recorded and replicated a three-day dietary food log prior to testing and fast 10–12 h prior to each visit. All T2DM were taking commonly prescribed a mixture of medication for glucose, lipid and/or blood pressure lowering medications (including Metformin, Lotensin HCT, Lovastatin, Glimepiride, Bydureon, Pravastatin, and Glipizide) and continued their prescriptions during the study. That said, T2DM subjects took their medications in the evening of each condition but were asked to withhold the medication the morning of the study. This study was conducted during the winter through the spring in Denton Texas, USA. Thus, it was assumed subjects were not heat acclimatized. This study was approved by the Texas Woman's University Institutional Review Board and was performed in agreement with the *Declaration of Helsinki*.

Table 1
Subject characteristics (mean ± SD).

	T2DM	HC
Number of subjects (male/female)	9 (3/6)	9 (2/7)
2 h glucose value during OGTT (mmol L^{-1})	*14.7 ± 3.5	5.9 ± 1.9
Age (y)	50.1 ± 12.0	41.1 ± 13.7
BMI (kg m^2)	*40.2 ± 7.4	26.4 ± 3.9
BSA (m^2)	*2.2 ± 0.29	1.8 ± 0.17
Fasting plasma glucose (mmol L^{-1})	*8.4 ± 2.9	5.2 ± 0.6
Fasting plasma insulin (pmol L^{-1})	94.9 ± 47	62 ± 46
Fat mass (kg)	*55.7 ± 25.3	25.7 ± 9.0
Fat mass (%)	45.0 ± 7.1	34.6 ± 7.9
HbA1c (%)	* 7.5 ± 1.8	5.3 ± 0.4
Height (cm)	167.8 ± 10	168 ± 8.7
Lean mass (kg)	65.8 ± 19.9	54.5 ± 23.1
Weight (kg)	*112.3 ± 26.9	74.0 ± 12.0

HbA1c, Hemoglobin A1c; BMI, body mass index; BSA, Body surface area.
* Statistically different from healthy control ($P<0.01$).

2.2. Experimental design

The experiment was a randomized repeated measures design. Following prescreening familiarization, all participants were randomized to complete a whole body passive heat stress trial and a no heating resting time control trial. Each trial was separated by at least 2 weeks in males and 4 weeks in females. For each condition, subjects rested in a seated position for 30 min at an ambient room temperature of 23.7 ± 1.0 °C and $56.5 \pm 0.1\%$ relative humidity for baseline measures. Following baseline data collection, subjects were then placed in a sling and either winch lifted into a water tank with water temperature set at 39.4 ± 0.3 °C and immersed to the clavicle or remained seated for 2 h under neutral ambient temperature. Following 1 h of hot water immersion, the participants were raised out of the water and rested in seated position for an additional 1 h, while being monitored during this recovery period. Immediately post immersion, a towel was given to dry off