EFFECTS OF AN ACUTE BOUT OF PASSIVE HYPERTHERMIA THERAPY ON GLYCEMIC CONTROL AND BLOOD PRESSURE RESPONSE IN HEALTHY INDIVIDUALS AND TYPE 2 DIABETICS

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ABSTRACT

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While exercise is beneficial, obese Type 2 diabetics (T2D) have very low exercise capacities. Research using passive heat stress utilizing hot tubs and saunas have reported improvements in cardiovascular and glycemic control in animal models. This project tested the hypothesis that an acute bout of hyperthermia will improve glucose and insulin responses and reduce arterial blood pressure during and following the exposure. Nine obese Type 2 diabetics (T2D; 50.1 ± 12 years, 7.5 ± 1.8% HbA1C) and nine similarly aged healthy controls (HC; 41.1 ± 13.7 years; $p = .185$, 5.3 ± 0.4%, HbA1C; $p = .007$) with similar resting blood pressures (T2D: 125 ± 27/ 77 ± 14, HC: 122 ± 14/ 81 ± 10 mmHg, $p > .05$) volunteered. Subjects underwent a whole body passive heated stress (1 hr resting in 39.4 ± 0.4 °C water) followed by 1 hr post immersion sitting recovery under normal ambient temperatures. Both groups were similarly heat stressed (Δ, core body, Tre, 1.4 ± 0.4°; Δ mean skin temperature, Tsk, 6.5 ± 0.8; and Δ heart rate, HR from rest, 33.5 ± 8.3 bpm) at the end of warm water immersion. No main interaction was found for group and condition for glucose, C-peptide, insulin, and leptin during a glucose tolerance test ($p > .05$). Additionally, in comparison to preimmersion values, there was no interactive effect for mean arterial blood pressure (MAP, time x group; $p = .145$). In both groups MAP was reduced ($p < .01$) from min 10 (Δ MAP, T2D: 10.2 ± 5.5, HC: 14.8 ± 8.4 mmHg)

through minute 60 of immersion (T2D: 12.8 ± 8.1, HC: 13.9 ± 11.2 mmHg) and remained below pre-immersion values ($p = .004$) up to 20 min post immersion (T2D: 10.8 ± 9.6, HC 7.6 ± 6.8 mmHg). These data indicate that an acute 1 hr bout of warm water immersion does not improve glucose and insulin responses 24 hr post treatment. However, passive hyperthermia results in similar hypotensive responses between groups and may offer a acute therapeutic benefit to both healthy and diabetic populations.

TABLE OF CONTENTS

Page

LIST OF TABLES

Table Page

LIST OF FIGURES

CHAPTER I

INTRODUCTION

The homeostatic relationship between storage and release of energy during fasting and feeding is an important normal metabolic function, which is predominately controlled by the action of insulin. β cells in the pancreatic islets of Langerhans secrete insulin in response to elevated blood glucose or amino acid levels following a meal. Insulin promotes the storage of glucose as glycogen in the liver and muscle, storage of amino acids in muscle proteins, and the accumulation of triglycerides in adipose tissue. When insulin fails to perform its physiological function, diabetes mellitus occurs; either by absolute lack of insulin production (type 1), or a relative insulin insufficiency associated with peripheral insulin resistance (Type 2). Mild and moderate insulin resistance is associated with obesity, age, and physical inactivity (Amati et al., 2009; Paolisso, Tagliamonte, Rizzo, & Giugliano, 1999; Ryan, 2000). The search for the molecular cause and a potential cure for Type 2 diabetes has taken two routes: the identification of gene mutations in family members with diabetes (Gloyn, 2003; Hussain, 2010; Shammas et al., 2013) or the investigation of the insulin signaling cascade (Chang, Chiang, & Saltiel, 2004; Frojdo, Vidal, & Pirola, 2009; Hall & Guyton, 2011; Kasuga, Karlsson, & Kahn, 1982; Myers & White, 1996; Paz et al., 1996; White, 2002; Wilden et al., 1992).

Efforts for identifying genes related to diabetes have been ongoing (Taylor, 1999) and would provide the simplest explanation for the disease; however, failure to reveal a

single mutation (Xu et al., 2013) suggest multiple defects are contributing and possibly a result of gene-environment interactions and epigenetics (Xu et al., 2013). Over consumption of food and physical inactivity are primary causes of obesity induced diabetes. The relationship between obesity and Type 2 diabetes is well established, and mounting evidence suggests that insulin signaling is impaired in obese insulin-resistant humans and rodents (Aguirre et al., 2002; Birnbaum, 2001; Gao et al., 2004; Hirosumi et al., 2002; Lee, Giraud, Davis, & White, 2003; Lee & White, 2004; Nguyen et al., 2005; Qiao, Zhande, Jetton, Zhou, & Sun, 2002; Wellen & Hotamisligil, 2005), caused by adipose tissue over production of cytokines. These cytokines contribute to a chronic inflammatory state and mediate insulin resistance and β cell function (Schaffer, 2003). Thus, peripheral and hepatic insulin resistance (Sheng & Yang, 2008), and impaired pancreatic β-cell function negatively influences blood glucose homeostasis (Alonso-Magdalena, Quesada, & Nadal, 2011). Uncontrolled hyperglycemia subsequently leads to a host of other complications such as damaging vascular and kidney function (Sakallioglu et al., 2007; Triplitt, 2012), which increases the risk for heart attack, stroke, blindness, amputation, and end-stage renal disease (Alwakeel, Al-Suwaida, Isnani, Al-Harbi, & Alam, 2009). Interventions to improve and control the complications of this disease include, exercise, diet, and pharmacological prescription.

Pharmacological intervention can improve glycemic control with such drugs as sulphonylureas, thiazolidinediones or exogenous insulin therapy, but does not prevent cardiovascular events, and may even increase risk in this population (Nissen & Wolski,

2007; Qi & Pekala, 2000). Moreover, side effects of insulin sensitizers (i.e., metformin) include gastrointestinal symptoms (Bell & Hadden, 1997), lactic acidosis (DePalo, Mailer, Yoburn, & Crausman, 2005), and renal failure (Berner et al., 2002). Thiazolidinediones, which lowers lipid agents and reduces hyperglycemia and hyperinsulinemia (Sotiropoulos et al., 2006), also have harmful side effects such as fluid retention, peripheral edema, weight gain, vascular abnormalities, and in rare instances congestive heart failure (Beltowski, Rachanczyk, & Wlodarczyk, 2013; Diamond, Bax, & Kaul, 2007; Hlatky & Bravata, 2007a, 2007b; Lebovitz & Banerji, 2001; Martens, Visseren, Lemay, de Koning, & Rabelink, 2002; Ogihara, Fujimoto, Nakao, & Saruta, 2010). Therefore, other therapies to control diabetes, such as exercise and diet are important.

Exercise is beneficial in maintaining optimal blood glucose, lipid, and blood pressure profiles, which prevent or delay chronic complications of diabetes (American Diabetes, 2010; Eriksson, 1999; Ostergard et al., 2006; Zanuso, Jimenez, Pugliese, Corigliano, & Balducci, 2010). This is due in part to short term effects of contracting muscle on glucose uptake as well as the lasting effect of contracting skeletal muscle on the action of insulin (Z. P. Chen et al., 2003; Frosig, Jorgensen, Hardie, Richter, & Wojtaszewski, 2004; Richter et al., 2004). Moreover, heat is a byproduct of exercise, and increases in internal heat load (i.e., core body temperature) may influence glucose homeostasis (Febbraio, 2001). Additionally, acute exercise under heat stress shifts fuel toward carbohydrate use and decreases fat utilization compared to exercise in cool

environments (Febbraio, Snow, Stathis, Hargreaves, & Carey, 1994a; Hargreaves, Angus, Howlett, Conus, & Febbraio, 1996; Mittleman, Ricci, & Bailey, 1998), perhaps due to sympatho-adrenal activity and/or increased intramuscular temperatures (Jimenez et al., 2007; Radomski, Cross, & Buguet, 1998). Consistent with this hypothesis, adaptations from repeated exposure to exercise in hot conditions (i.e. heat acclimation) reduces muscle glycogen utilization, rates of carbohydrate utilization, and increases free fatty acid uptake (Kirwan et al., 1987). Thus, passive hyperthermia or exercise during heat stress may increase carbohydrate metabolism and improve these functions that are impaired in obese Type 2 diabetics.

Research suggests an influential relationship between "stress proteins", commonly termed heat shock proteins (HSPs) and insulin sensitivity (Chung et al., 2008; Gupte, Bomhoff, Touchberry, & Geiger, 2011; Hooper, 2009) in animal models of obesity induced diabetes (Bathaie, Jafarnejad, Hosseinkhani, & Nakhjavani, 2010; Burkart, Germaschewski, Schloot, Bellmann, & Kolb, 2008; H. W. Chen et al., 1995; Chung et al., 2008; Kondo et al., 2012; Najemnikova, Rodgers, & Locke, 2007). Heat shock proteins provide cytoprotection that may combat protein damage and reduce apoptosis, suppress proinflammatory cytokines, repair ion channels, and aid in protein folding (Benjamin & McMillan, 1998) that may be attenuated in diabetes. In fact, decreases in HSPs may be a primary factor resulting in the development of diabetes and accompanying widespread organ damage (Hooper, 1999, 2009). There is strong evidence that intracellular HSPs are lower in Type 2 diabetics compared to healthy controls, and are associated with insulin

resistance (Bruce, Carey, Hawley, & Febbraio, 2003; Figueredo et al., 1996; Kavanagh, Zhang, & Wagner, 2009; Rodrigues-Krause et al., 2012). This is supported by decreases in HSF-1 gene expression (Atalay et al., 2004; Bruce et al., 2003; Kurucz et al., 2002; McClung et al., 2008; Nakhjavani et al., 2012; Rodrigues-Krause et al., 2012) and HSP72 mRNA (Kurucz et al., 2002) in diabetic humans and animals. Consistent with those findings, decreased expression of HSP72 in skeletal muscle is correlated with insulin resistance in patients with Type 2 diabetes (Kurucz et al., 2002). Moreover, obesity-driven inflammation promotes insulin resistance, which itself reduces the expression of HSPs and increases harmful protein aggregates. Finally, a reduction of HSPs damages the pancreatic beta cell which further disrupts insulin signaling and increases inflammation (Hooper, 2003; Hooper & Hooper, 2005). The primary means by which HSPs can be induced are pharmacological interventions, exercise, and heat stress (Geiger & Gupte, 2011). Given these findings, increasing the induction of HSPs, by either exercise, or heat stress, may be a viable approach to improve glycemic control in susceptible populations, as proposed by others (Bathaie et al., 2010; Bruce et al., 2003; H. W. Chen, Chen, Tsai, & Yang, 1999; Chung et al., 2008; Geiger & Gupte, 2011; Gupte, Bomhoff, Morris, Gorres, & Geiger, 2009; Gupte, Bomhoff, Swerdlow, & Geiger, 2009; Gupte et al., 2011; Hooper, 1999, 2003, 2009; Hooper & Hooper, 2005; Kavanagh, Flynn, Jenkins, Zhang, & Wagner, 2011; Kurucz et al., 2002; Rodrigues-Krause et al., 2012). Given the beneficial responses of heat stress (i.e., “heat therapy”) in improving glycemic control in animal models (Bathaie et al., 2010; Chung et al., 2008; Gupte, Bomhoff, Swerdlow, et

al., 2009; Kavanagh et al., 2011), such therapy may be equally favorable in humans who have diabetes.

Aims of the Study/ Problem Statement

The proposed study will investigate a hypothesized influence of passive heat stress on improving glycemic and short term blood pressure control in obese Type 2 diabetics. Information from such findings would be useful towards the treatment of Type 2 diabetes, and associated comorbidities (i.e., hypertension, cardiac disease, obesity). While exercise is beneficial (American Diabetes, 2010; Eriksson, 1999; Ostergard et al., 2006), diabetics have very low exercise capacities (Kadoglou et al., 2009; Leite, Monk, Upham, & Bergenstal, 2009). Interestingly, passive hyperthermia treatments may offer similar benefits comparable to exercise, thus suggesting a novel alternative approach for improving the damaging conditions from diabetes (Hooper, Balogh, Rivas, Kavanagh, & Vigh, 2014). Repeated passive heat stress improves vascular endothelial function (D. J. Green et al., 2010; Naylor et al., 2011), mitochondria biogenesis (C. T. Liu & Brooks, 2012) and myocardial function (Donnelly, Sievers, Vissern, Welch, & Wolfe, 1992; Gowda et al., 1998). Likewise, obesity induced diabetic animal models have reported a single (Gupte et al., 2011) and repeated heat treatment, via warm bath immersion, improves glucose tolerance and skeletal muscle insulin signaling (Bathaie et al., 2010; Chung et al., 2008; Gupte, Bomhoff, Swerdlow, et al., 2009; Kavanagh et al., 2011). Most importantly, a few human studies have also reported that sauna and hot bath therapy altered endothelial function, reduced body weight, blood pressure, and fasting

plasma glucose in obese hypertensive and chronic heart failure and diabetic patients (Biro, Masuda, Kihara, & Tei, 2003; Hooper, 1999; Miyata et al., 2008; Shin, Wilson, & Wilson, 2003). To date only one preliminary human study (Hooper, 1999) investigated the effects of repeated heat "therapy" at rest (i.e., 30 min passive heat exposure for 6 days a week for 3 weeks), via hot-tub immersion, on markers of glycemic control in Type 2 diabetes. This therapy reduced mean fasting plasma glucose (181.8 ±36.0 to 158.4±41.4 mg/dL) and glycosylated hemoglobin (from 11.3±3.1% to 10.3±2.6%). Despite a number of animal studies demonstrating beneficial effects of heat therapy, no other human trials have investigated the influence of heat stress, or the mechanisms of those perturbations in improving glycemic control or hypertension. This study will investigate the influence of an acute bout of passive hyperthermia on glycemic control and blood pressure responses. The objective will be accomplished by addressing the following two specific Aims:

Aim 1) will test the hypothesis that an acute bout of passive heat stress will improve glucose tolerance and insulin responses, as evidenced by a reduction in the area under the curve for a 2 hr oral glucose tolerance test; and

Aim 2) will test the hypothesis that an acute bout of passive heat stress will induce acute reductions in arterial blood pressure as evidenced by decreased area under the curve blood pressure measures during and post heat stress.

Definitions

Protein Kinase B (Akt) – Also known as Akt, is a serine/threonine-specific protein kinase that plays a key role in multiple cellular processes such as glucose metabolism, apoptosis, cell proliferation, transcription and cell migration (Zou, Li, Li, & Cui, 2000).

5' Adenosine Monophosphate-Activated Protein Kinase – Also known as AMPK is an enzyme that plays a role in cellular energy homeostasis. The net effect of AMPK activation is stimulation of hepatic fatty acid oxidation and ketogenesis, inhibition of cholesterol synthesis, lipogenesis, and triglyceride synthesis, inhibition of adipocyte lipolysis and lipogenesis, stimulation of skeletal muscle fatty acid oxidation and muscle glucose uptake, and modulation of insulin secretion by pancreatic beta-cells (Winder & Hardie, 1999).

Area Under the Curve (AUC) represents the total amount of glucose absorbed by the body, irrespective of the rate of absorption. AUC becomes useful for knowing the average concentration over a time interval, AUC/t. Also, AUC is referenced when talking about elimination. The amount eliminated by the body = clearance (volume/time) * AUC (mass*time/volume).

Glucose Transport 4 Protein (GLUT4) is a protein that in humans is the insulin-regulated glucose transporter found in adipose tissues and striated muscle (skeletal and cardiac) that is responsible for insulin-regulated glucose transport into the cell (Huang & Czech, 2007).

Glycosylated Hemoglobin (HbA1c) is a form of hemoglobin that is measured primarily to identify the average plasma glucose concentration over prolonged periods of time (i.e. months). It is formed in a non-enzymatic glycation pathway by hemoglobin's exposure to plasma glucose. Higher amounts of glycated hemoglobin, indicating poorer control of blood glucose levels, have been associated with cardiovascular disease, nephropathy, and retinopathy (Larsen, Horder, & Mogensen, 1990).

Heat Shock Factor 1 (HSF1) is a protein that in humans is encoded by the HSF1 gene, which is the master regulator of increasing heat shock proteins (Rabindran, Giorgi, Clos, & Wu, 1991)

Heat Shock Protein (HSP) are a group of proteins induced by exposure to elevated temperatures or other stress and are an important key part of the heat shock response and is induced primarily by heat shock factor (HSF1) gene. The most prominent members of this group are a class of functionally related proteins involved in the folding and unfolding of other proteins (Wu, 1995). Heat-shock proteins are named according to their molecular weight. For example, Hsp60, Hsp70 and Hsp80 (the most widely-studied HSPs) refer to families of heat shock proteins on the order of 60, 70, and 80 kilodaltons in size, respectively. The small 8-kilodalton protein ubiquitin, which marks proteins for degradation, also has features of a heat shock protein (Raboy, Sharon, Parag, Shochat, & Kulka, 1991)

Nuclear factor kappa B (NF-κB) are transcription factors coordinating regulators of immune and inflammatory responses. They also play a pivotal role in oncogenesis and metabolic disorders (Tornatore, Thotakura, Bennett, Moretti, & Franzoso, 2012).

Insulin Sensitivity describes how sensitive the body is to the effects of insulin. Insulin sensitive cells will require smaller amounts of insulin to lower blood glucose levels than someone who has low sensitivity.

Insulin Signaling Cascade are the events such as perception and transmission of the signal, passing on the "message", arrival of the "message", and response by the cell so the outcome is appropriate (movement of GLUT 4 protein to the cell membrane) to the original signal of the insulin hormone (Hancock, 2010).

Insulin Receptor Substrate (IRS) plays a key role in transmitting signals from the insulin and insulin-like growth factor-1 (IGF-1) receptors to intracellular pathways PI3K / Akt and Erk MAP kinase pathways and play important biological function for both metabolic and mitogenic (growth promoting) pathways (Sun et al., 1991).

C-Jun N-Terminal Kinase (JNK) also known as stress-activated protein kinases, consist of ten isoforms derived from 3 genes: JNK1 (four isoforms), JNK2 (four isoforms) and JNK3 (two isoforms) are associated with inflammatory signals, changes in levels of reactive oxygen species, ultraviolet radiation, protein synthesis inhibitors, and are considered to be a key regulator of various inflammatory pathways (Cui, Zhang, Zhang, & Xu, 2007; Vlahopoulos & Zoumpourlis, 2004).

Oral Glucose Tolerance Test (OGTT) is a test that measures the body's ability to use sugar, called glucose, and is used to diagnose prediabetes and diabetes (Sacks, Arnold, Bakris, Bruns, Horvath, Kirkman, Lernmark, Metzger, Nathan, et al., 2011).

Rating of Perception of Thermal Sensation is a number scale developed for the assessment of subjective thermal responses supporting physiological responses (Dadgar et al., 2010)

Tumor Necrosis Factor Alpha (TNFα) is an adipokine involved in systemic inflammation and is a member of a group of cytokines that stimulate the acute phase reaction. It is produced chiefly by activated macrophages (M1), although it can be produced by many other cell types such as CD4+ lymphocytes, NK cells and neurons (Szlosarek & Balkwill, 2003).

Waist Circumference is a measure of the distance around the abdomen and is one of the most practical tools to assess abdominal fat for chronic disease risk (American College of Sports Medicine., Thompson, Gordon, & Pescatello, 2010).

Assumptions

The assumptions of this investigation will be:

1. Participants in the diabetic group will be nonsmoking, sedentary, obese, Type 2 diabetic and not on insulin therapy.
2. Participants in the healthy group will be nonsmoking, sedentary, non-obese, not diabetic.
3. Participants will correctly and honestly fill-out their diet records and

consume the given standard meal the evening prior to each experiment.

4. Participants will fast at least 12 hr prior to all blood draws.
5. Participants will refrain from exercising 3 days prior to each experiment and vigorous exercise 7 days prior to each experiment.
6. Participants will refrain from alcohol consumption and smoking during all experimental protocols.
7. Participants will not change weight over the course of the study.

Limitations

1. Oral Glucose Tolerance Test. We recognize that the gold standard for measuring insulin sensitivity is the euglycemic hyperinsulinemic clamp (Sacks, Arnold, Bakris, Bruns, Horvath, Kirkman, Lernmark, Metzger, & Nathan, 2011). However, studies have shown strong correlations between the results of an OGTT and the euglycemic hyperglycemic clamp (predicting the metabolic clearance rate of glucose r = .80; insulin sensitivity index, r = .79 - .86 (Soonthornpun et al., 2003; Stumvoll et al., 2000)).

Delimitations

1. Recruitment. Participants will be limited to Dallas-Fort Worth and Metroplex surrounding communities.

Significance of the Study

Obesity is a global, costly, and a preventable medical condition that affects most age groups, both genders, and all ethnic groups (Fakhouri, Ogden, Carroll, Kit, & Flegal,

2012; Howel, 2012; Ogden, Carroll, Kit, & Flegal, 2012; Rendall, Weden, Fernandes, & Vaynman, 2012; Sardinha et al., 2012; H. L. Walls et al., 2012) and its incidence has more than doubled since 1980. In 2008, more than 1.4 billion adults were classified as overweight, with 2.8 million adults dying each year from obesity-related complications, including diabetes (Organization, 2012). The United States leads the world with greater than one third (35.7%) of adults and 17% of youth classified as obese (Ogden et al., 2012).

According to The Centers for Disease Control and Prevention (CDC), diabetes is the seventh leading cause of death in the United States, affecting 25.8 million people (8.3% of the U.S. population). The numbers of diagnosed cases of diabetes have doubled from 1980 to 2004. These estimates are projected to double within the next 15 to 20 years due in part to: (1) sedentary lifestyle and poor nutrition, (2) growth of ethnic populations who are at a greater risk of developing diabetes , and (3) aging of the population (Florez et al., 2012; Goldberg & Mather, 2012). The risk for death among people with diabetes is about twice that of people of similar age without diabetes. Additionally, diabetes is proposed to be underreported because the actual cause of death from other comorbities (ie., stroke, infarction) are reported on death certificates (Prevention, 2011). Estimated diabetes-related costs in the United States in 2007 totaled (direct and indirect) $174 billion (Prevention, 2011).

Type 2 diabetes is associated with a high prevalence of cardiovascular comorbidities, hypertension, stroke, cardiac disease, neurological disorders, and a

reduced exercise tolerance and capacity (Sacks, Arnold, Bakris, Bruns, Horvath, Kirkman, Lernmark, Metzger, & Nathan, 2011). The American Diabetes Association recommends at least 150 min/week of vigorous aerobic exercise ("Standards of medical care in diabetes--2007," 2007). However, because individuals with diabetes have a lower exercise capacity, vigorous activity and/or increasing the duration of exercise may not be feasible. Thus, heat stress during rest or low intensity exercise combined with heat stress may offer a potential therapeutic modality that may be of similar benefit as high intensity exercise or medications that aim to reduce blood glucose levels in the Type 2 diabetes population.

This project will investigate the influence of an acute bout of passive hyperthermia therapy on glucose and insulin and blood pressure responses in obese Type 2 diabetic adults. The proposed study is significant because it will investigate a novel therapy (acute bout of heat stress) on improving glycemic control and short-term blood pressure profiles in Type 2 diabetic adults. If the proposed hypotheses are correct, this modality may be incorporated as a treatment to improve glycemic and blood pressure control and possibly reduce comorbidities of diabetes.

CHAPTER II

REVIEW OF THE LITERATURE

The purpose of this study was to determine if passive hyperthermia therapy at rest will improve insulin responses and glucose tolerance in obese Type 2 diabetics. A second purpose is to determine if hyperemia therapy improves acute blood pressure profiles during and post heat stress. Therefore, the following chapter reviews the literature in which the studies relate to (a) obesity induced diabetes, (b) lipotoxicity, inflammation, and impaired insulin signaling, (c) physical inactivity and diabetes, and (d) exercise mimetics and hyperthermia therapy.

Obesity Induced Diabetes

Over consumption of food and decrease physical activity is associated with diabetes mellitus. Obesity-induced diabetes is increasing at epidemic rates. In 2008, more than 1.4 billion adults were classified as overweight, with 2.8 million adults dying each year from obesity-related complications, including diabetes, resulting in the fifth leading risk for global deaths (Centers for Disease Control and Prevention, 2012).

Diabetes mellitus is characterized as an impairment of insulin production or action, or both, which causes high levels of blood glucose levels. As a result, blood glucose concentrations increase (hyperglycemia), cellular glucose utilization falls progressively lower, and utilization of fats and proteins increase (Hall & Guyton, 2011). The complications of hyperglycemia cause exertion of large amounts of osmotic pressure in

the extracellular space, which can cause cellular dehydration (Popli et al., 2013). Excessively high levels of glucose are lost through the urine causing osmotic diuresis by the kidneys and depletion of body fluids and electrolytes (Steenkamp, Alexanian, & McDonnell, 2013). Long term uncontrolled hyperglycemia causes injury in many tissues, particularly blood vessels. Uncontrollable diabetes mellitus leads to increased incidence of heart attack, stroke, renal disease, and blindness (Hall & Guyton, 2011; Sacks, Arnold, Bakris, Bruns, Horvath, Kirkman, Lernmark, Metzger, & Nathan, 2011; Steenkamp et al., 2013).

The etiology of Type 2 diabetes is currently not well understood. However, evidence is gaining on a progressive insulin resistance due to a disruption of pancreatic β-cell function with chronic damage and the loss of β-cell mass (Alonso-Magdalena et al., 2011). A major contributor is an overabundance of circulating fatty acids, which induces a pro-inflammatory state and contribute to lipotoxicity and multisystem organ failure (Eckel, Grundy, & Zimmet, 2005; Navina et al., 2011). Chronically elevated fatty acids are associated with a state of low grade chronic inflammation, as well as peripheral and hepatic insulin resistance (Furuhashi, Ishimura, Ota, & Miura, 2011; Sheng & Yang, 2008), which impairs normal cell signaling. Moreover, the disruption of cell signaling may signal apoptotic cell death (Schaffer, 2003). Triglycerides stored in fat cells release plasma-free fatty acids via cyclic AMP-dependent enzyme hormone sensitive lipase (Eckel et al., 2005). Lipoprotein lipase has also been suggested to increase fatty acids by lipolysis of triglyceride-rich lipoproteins (Eckel et al., 2005). When insulin resistance

develops in fat cells, adipose tissue increases fatty acid synthesis and inhibits the anti-lipolytic effect of insulin (Castan-Laurell, Dray, Knauf, Kunduzova, & Valet, 2012). Thus, fatty acids continue to rise in blood due to insulin resistance in fat tissue. Hormones, cytokines, and bioactive lipids activate meta-inflammation by the responses that regulate each other by the same cellular signaling pathways (Furuhashi et al., 2011) that may negatively influence blood-glucose homeostasis.

Lipotoxicity and Inflammation

Accumulation of excess lipids in non-adipose tissue leads to cell dysfunction or cell death (Schaffer, 2003). The phenomenon, known as lipotoxicity is described by the accumulation of fats stored in nonfat tissue that impaire cell function, contributes to diabetes and heart failure in humans (Schaffer, 2003).

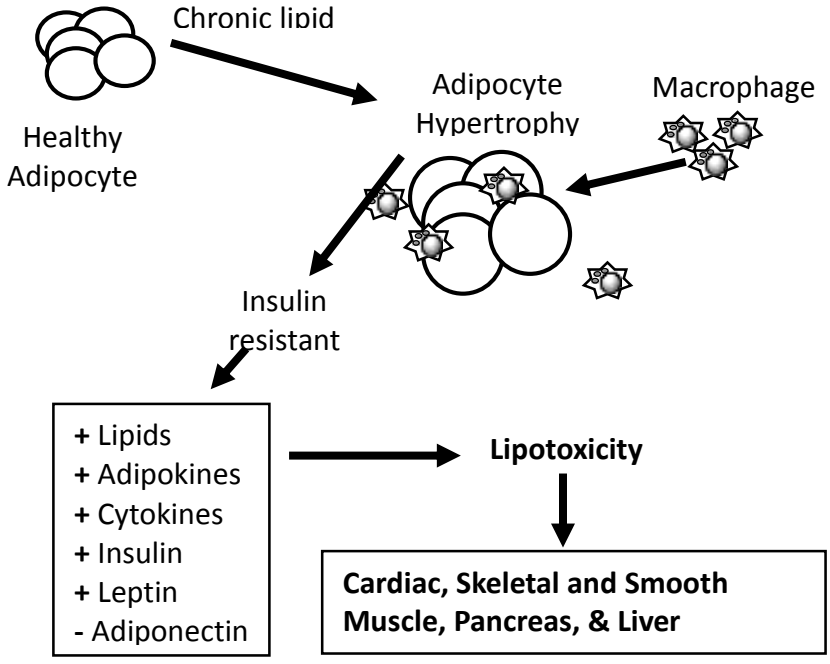

Figure 1. Lipotoxic effect on other tissues

Accumulation of body fat or adipose tissue in obese individuals was once thought to be only a fuel storage site. However, research now recognizes adipose tissue as an important endocrine organ that can release hormones, which communicate to the brain and peripheral tissues that regulate appetite and metabolism (Schaffer, 2003). Plasma free fatty acids (FFA) play important roles in skeletal muscle, heart, liver, and pancreas. Other than secreting FFA, adipose tissue produces and excretes many proteins and molecules with autocrine, paracrine, and endocrine functioning that regulate energy intake and energy expenditure, glucose and lipid metabolism, as well as inflammation (Lihn, Pedersen, & Richelsen, 2005). Additionally, obesity is associated with chronically elevated plasma free fatty acid (FFA) which may induce peripheral and hepatic insulin resistance (Sheng & Yang, 2008) and a state of low grade chronic inflammation (Furuhashi et al., 2011). Prolonged metabolic inflammation is observed in individuals with metabolic disease, obesity, Type 2 diabetes, and cardiovascular disease (Furuhashi et al., 2011). Excess fatty acids may also impair normal cell signaling and induce apoptotic cell death (Schaffer, 2003).

Over consumption of foodstuff is associated with obesity increases in triglycerides (TG) in adipose tissue. TG are also stored in non-adipose tissue (ie., muscle, liver, pancreas, and heart) which is termed ectopic fat deposition (van Herpen & Schrauwen-Hinderling, 2008). Ectopic lipid accumulation is associated with impaired functioning in muscle, liver, pancreas and heart, which leads to the development of Type 2 diabetes and risk factors for cardiovascular disease (van Herpen & Schrauwen-Hinderling, 2008).

Lipid accumulation is also suggested to occur by increasing fatty acid synthesis within tissues or reduced fatty acid oxidation/disposal (Shulman, 2000).

Increased intramyocellular lipid (IMCL) accumulation increases risk for Type 2 diabetes and correlated strongly to insulin resistance (Jacob et al., 1999; Krssak et al., 1999). In mice fed a high fat diet for 12 weeks, the accumulation of bioactive lipid species rapidly impairs hepatic insulin action and skeletal muscle insulin resistance (Turner et al., 2013). Glucose intolerance was developed as soon as 3 days, whole body insulin resistance was observed after 1 week, adipose developed insulin resistance within 1 week and skeletal muscle by 3 weeks. Tissue specific diacylglycerol increased in the liver and muscle during insulin resistance and adipose tissue was associated with an increase in ceramide and sphingomyelin (Turner et al., 2013). Furthermore, it has been shown that lipid intermediates ceramide, sphingolipid, and diacylglycerol (DAG) is higher in insulin resistant compared to insulin sensitive subjects particularly in type I fibers (Coen et al., 2010).

In contrast to sedentary obese individuals, a paradox on accumulation of intramuscular fat is observed in endurance trained populations that shown high IMCL and are insulin sensitive (Hardin et al., 1995; van Loon & Goodpaster, 2006). However, the difference is the supply and demand between the obese over consumer and the endurance trained adaptive population. The endurance trained continually use and restore, while the sedentary only store intramuscular fat. An increase in IMCL storage has been attributed to a positive fat balance due to 2 to 8 weeks of a high fat diet (Dorfman et al., 2009; Hill

et al., 1991). Moreover, it has been reported that intravenous infusion of FFA in healthy males increased IMCL and decreased insulin sensitivity similar to a 3 day high fat diet compared to a low fat diet (Bachmann et al., 2001). Interestingly, the endurance trained population adapts to a demand-driven IMCL causing increases in fat oxidation and low lipid intermediates such a as diacylglycerol (DAG), ceramide, and acyl-CoA (Kelley & Mandarino, 2000). In contrast, the obese sedentary have high fat and low oxidative capacity contribute to an increase level of these intermediates (Hulver et al., 2003; van Herpen & Schrauwen-Hinderling, 2008). DAG has been suggested to disrupt insulin action via increasing inflammatory pathways via protein kinase C (PKC) (Itani, Ruderman, Schmieder, & Boden, 2002) and is associated with insulin resistance in humans (Itani et al., 2002; Magkos et al., 2012).

Downregulation of diaclyglycerol kinase delta expression (phopsphorylates diacyglycerol) is observed in Type 2 diabetes which reduces insulin sensitivity, insulin signaling and glucose transport (Chibalin et al., 2008). Impaired glucose uptake has also been associated with lipid intermediates activating PKC, which activates serine/threonine of the insulin receptor substrates (IRS-1 and IRS-2) on Ser307 phosphorylation and decreases tyrosine phosphorylation (Hulver & Dohm, 2004; Yu et al., 2002). Ceramide, another contributor of insulin resistance in humans and rodents (Adams et al., 2004; Bruce et al., 2012) decreases the activation of Akt (Adams et al., 2004; Powell, Turban, Gray, Hajduch, & Hundal, 2004; Schmitz-Peiffer, Craig, & Biden, 1999) while activating c-Jun terminal kinase (JNK) (Chiu, Sun, Koshkina, & Klip, 2013; Jurczak et al., 2012).

These proteins that activate inflammatory pathways trigger an immune response termed metabolic triggered inflammation, or "meta-inflammation." Hormones, cytokines, and bioactive lipids are activating meta-inflammation by metabolic and immune responses that regulate each other by the same cellular machinery (Furuhashi et al., 2011). These cellular responses target metabolically critical organs and tissues including adipocytes and macrophages which adversely affect systemic homeostasis (Furuhashi et al., 2011). Extracellular (cytokines, lipids, fatty acids) as well as intracellular mediators (endoplasmic reticulum stress an excess production of reactive oxygen species) initiate metabolically active cells. Obesity may be associated with an imbalance of pro and anti-inflammatory cytokines (Aprahamian & Sam, 2011). A two to four fold increase in proinflammatory and anti-inflammatory cytokines, cytokine agonists, as well as increases in macrophages, neutrophils and natural killer cells are indicative of systemic low grade inflammation (Bruunsgaard et al., 2003; Bruunsgaard, Pedersen, Schroll, Skinhoj, & Pedersen, 1999; Bruunsgaard & Pedersen, 2003; Chawla, 2010).

Macrophage tissue infiltration is a significant contributor of inflammation in obese insulin resistant populations (Qatanani & Lazar, 2007; Weisberg et al., 2003). The two most studied macrophage subtypes are classically activated macrophages (M1) and macrophage (M2a). M1 are activated by interferon-y or endotoxin, which promotes an interleukin-12-mediated T helper 1 immune response and releases cytokines such as IL-1β, IL-6, and TNKα inducing a pro-inflammatory state. The M2a are induced by

Interleukin 4 or 13, immune regulation, and anti-inflammatory cytokines IL10, wound healing, or tissue repair (Han et al., 2013). The pro-inflammatory M1 state has been attributed to blocking adipocyte insulin action, obesity induced insulin resistance, causing type 2 diabetes (Harford, Reynolds, McGillicuddy, & Roche, 2011). In contrast healthy lean individual's macrophages are in the alternatively activated M2 state (Han et al., 2013; Harford et al., 2011). Genes JNK1 and JNK2 encode for JNK proteins and are activated by obesity and cause insulin resistance (Sabio & Davis, 2010). It has been shown that JNK1 in the hypothalamus is required for high-fat diet induced obesity and both JNK1 and JNK2 specific macrophages are associated with insulin resistance (Han et al., 2013). Control (with JNK1/2) wild type mice and macrophage-specific deficient of JNK mice (knockout mice) were fed normal chow, and both displayed similar glucose and insulin responses. However, when fed a high fat diet, the wild type developed hyperglycemia, hyperinsulinemia, and intolerance to glucose and insulin. The knockout mice were protected against the high fat diet suggesting that macrophage specific JNK deficiency prevented the negative effects and remained insulin sensitive. Furthermore, it was observed that the high fat diet decreased Akt activation in the liver, adipose tissue, and muscle in wild type but not the knockout mice. In the wild type mice, β cell proliferation, islet hypertrophy, and suppression of glucose stimulated insulin secretion was also suppressed compared to knockout mice. This data suggest that JNK macrophages induced from a high fat diet causes accumulation of adipose tissue macrophages and M1 polarization (Han et al., 2013).

Additionally, the cytokine adiponectin, which can regulate inflammation are produced by adipose tissue, and is elevated in lean and healthy populations (Aprahamian & Sam, 2011). Under disease states such as coronary artery disease (Shibata, Murohara, & Ouchi, 2012), diabetes mellitus (Inoue, Maehata, Yano, Taniyama, & Suzuki, 2005)) and increased body mass (Arita et al., 2012), adiponectin levels decline. Adipocyte hypertrophy found in obese populations have shown to produce low levels of adiponectin and higher levels of pro-inflammatory cytokines, such as TNF-α (Berg & Scherer, 2005). Thus, adiponectin has the potential to decrease the inflammatory process. In contrast, adipokines that induce a pro-inflammatory response (leptin, TNF-α, PAI type 1, IL-1β, IL-6, and IL-8) are increased in obese individuals (Berg, Combs, Du, Brownlee, & Scherer, 2001; Berg & Scherer, 2005). Utilizing models of overexpression and knockout adiponectin receptor, AdopoR1, adiponection has been suggested to play a role in glucose uptake and insulin sensitivity in obesity induced rats (Fruebis et al., 2001; Patel et al., 2012) and adiponectin knockout mice (Maeda et al., 2002).

Systemic inflammation and elevated cytokines are associated with obesity and insulin resistance (Duncan et al., 2003; Hunter, 2012; Zeyda & Stulnig, 2009). C-reactive protein (CRP) and tumor necrosis factor- α (TNF-α) are measures of systemic inflammation and are elevated in obesity, Type 2 diabetes, and coronary artery disease. (Engeli et al., 2003; Ouchi et al., 2003). C-reactive protein (CRP) is an acute phase protein synthesized primarily in the liver that arises in response to inflammation and associated with Type 2 diabetes, insulin resistance, obesity and other characteristics of

the metabolic syndrome (Ford, 1999; Pradhan, Cook, Buring, Manson, & Ridker, 2003; Pradhan, Manson, Rifai, Buring, & Ridker, 2001). In rat L6 skeletal muscle cell cultures, CRP caused a decrease in insulin stimulated glucose transporter 4 (GLUT4) and was associated with elevated IRS-1 phosphorylation at Ser307 and Ser612 as well as activation of both JNK and ERK 1/2 activity (D'Alessandris, Lauro, Presta, & Sesti, 2007). When treated with JNK and ERK 1/2 inhibitors, reversal of insulin stimulated phosphorylation of IRS-1 at Try632 was observed. CRP overexpression transgenic mice contributes to insulin resistance and hepatosteatosis in high fat-fed mice (Kaneko et al., 2011). In human mononuclear cells, CRP induces the production of tumor necrosis factor (TNF-α) (Nabata et al., 2008) and inhibits adiponectin gene expression in adipocytes (G. Yuan et al., 2007) and disrupts the binding of leptin to its receptor in cultured cells and ob/ob mice (K. Chen et al., 2006).

The pro-inflammatory cytokine tumor necrosis factor- α (TNF-α) in skeletal muscle (Saghizadeh, Ong, Garvey, Henry, & Kern, 1996), adipose tissue (Kern, Ranganathan, Li, Wood, & Ranganathan, 2001), and plasma (Mishima et al., 2001; Zinman, Hanley, Harris, Kwan, & Fantus, 1999) is associated with Type 2 diabetes (Plomgaard et al., 2005). In cultured human cells, TNF-α can impair insulin stimulated glucose uptake (Halse, Pearson, McCormack, Yeaman, & Taylor, 2001) and whole body glucose transport in rats (Youd, Rattigan, & Clark, 2000). Furthermore, TNF-α has been shown to increase serine 307 phosphorylation of IRS-1 in cultured cells (Hotamisligil et al., 1996; Paz et al., 1997) and rodents (Hotamisligil, Budavari, Murray, & Spiegelman,

1994). When TNF-α was infused for 1h in healthy humans, this directly inhibited insulin signaling through the inactivation of Akt substrate 160 phosphorylation in skeletal muscle (Plomgaard et al., 2005). Plomgaard et al. (2005) also showed an increase in serine 312 phosphorylation of IRS-1 mediated by c-Jun N-terminal kinase (JNK), a protein that is associated with inflammatory signaling (Aguirre, Uchida, Yenush, Davis, & White, 2000; Aguirre et al., 2002; Tanti et al., 2004).

The mitogen-activated protein kinases (MAPKs), which include c-Jun N-terminal kinase (JNK), extracellular signal-regulated kinase (ERK) 1/2, and p38 MAPK are involved with a varied list of cellular stimuli, such as mitogens, osmotic stress, heat shock, and pro-inflammatory cytokines and can influence gene expression, differentiation, cell survival, and apoptosis (Pearson et al., 2001). Moreover they can alter insulin signaling transduction (Aguirre et al., 2000; Aguirre et al., 2002; Plomgaard et al., 2005; Tanti et al., 2004; Xi et al., 2011; Yeo, Yang, Li, & Lim, 2012). In vitro, JNK induces insulin resistance due to serine kinase activation and is moderately improved with a selective JNK inhibitor (Santos, Diamond-Stanic, Prasannarong, & Henriksen, 2012). Both JNK and ERK 1/2 are activated by angiotensin II and inhibits glucose uptake in vascular smooth muscles which activate Ser307 and Ser616 (Izawa et al., 2005) However, when ERK and JNK inhibitors are added, angiotensin II induced Ser307 and Ser616 phosphorylation of IRS-1 is reversed. Moreover, p38 MAPK activity increases in response to inflammatory cytokines (Zarubin & Han, 2005) and stimulates hepatic glucose production (Z. Liu & Cao, 2009) In vitro, oxidative stress stimulates p38 MAPK

mechanisms and decrease glucose transport activity via loss of IRS-1/2 proteins and increase in IRS-1 Ser307 phosphorylation. Moreover, inhibition of p38 MAPK restored oxidative stress induced loss of IRS-1 protein (Archuleta et al., 2009).

In summary, a relationship seems to exist between chronic inflammation, obesity, and insulin resistance through inflammatory cytokines, which activate the serine-threonine kinases (JNK) and an inhibitor of k B kinase (IKK) that can impair function of the insulin receptor. Furthermore, the interference of downstream signaling is observed in insulin responsive organs (liver, skeletal muscle, and adipose tissue). Impaired insulin action may be caused by elevated lipid metabolites (ceramide and diacylglycerol) which can directly activate JNK and IKK (Hooper, 2009). These studies provide strong evidence that inflammatory cytokines disrupt signaling pathways with the up regulation of certain isoforms of protein kinase C (PKC), c-Jun N-terminal kinase (JNK), and nuclear factor-kappa B (NF-kB).

Impaired Insulin Signaling

The previously mentioned pro-inflammatory proteins can cause impaired downstream insulin signaling. Within normal healthy cells, insulin binds to the cell-surface receptor activating the tyrosine kinase domain which auto-phosphorylates the β subunit where tyrosine kinase residues are phosphorylated and amplification of the signal occurs (Kasuga et al., 1982; Wilden et al., 1992). This leads to rapid phosphorylation of the insulin receptor substrates (IRS) -1 & -2, attracts multiple signaling intracellular

intermediates (Myers & White, 1996; Paz et al., 1996), and most importantly recruits the glucose transporter (GLUT4) from the vesicles to the cell membrane, which allows glucose into the cell (Frojdo et al., 2009; Hall & Guyton, 2011). The IRS-1&2 are important with respect to diabetes in that a defect in the IRS proteins contributes to insulin resistance (Chang et al., 2004; White, 2002). For example, IRS knockout mice are markedly insulin resistant (White, 2002). Moreover, obesity and chronic inflammation cause the tyrosine phosphorylation of the IRS to become defective (Lee & White, 2004; Wellen & Hotamisligil, 2005). Serine hyper-phosphorylation (see Table 1), caused by a number of intracellular inflammation kinases listed in table 1 (including JNK) can impair components of the insulin signaling cascade in human and animal models of insulin resistance (Aguirre et al., 2002; Birnbaum, 2001; Qiao et al., 2002).

Table 1

Causes of IRS-1 Hyper-Serine Phosphorylation

Insulin resistance: Causes	
JNK	(Gao et al., 2004; Hirosumi et al., 2002; Lee et al., 2003; Nguyen et al., 2005) **Stress, Hyperlipidemia** **Inflammation, Obesity**
IKKβ	(Kamon et al., 2004; Shoelson, Lee, & Yuan, 2003; M. Yuan et al., 2001) **Inflammation**
TNFα	(Hotamisligil et al., 1996; Hotamisligil, Shargill, & Spiegelman, 1993; Hotamisligil & Spiegelman, 1994; Qi & Pekala, 2000; Uysal, Wiesbrock, Marino, & Hotamisligil, 1997) **Inflammation, Obesity**

Note: Modified from Draznin, 2006.

Physical Inactivity and Type 2 Diabetes

Physical inactivity (Dubbert et al., 2002; Fletcher, 1999; Kruger, Venter, Vorster, & Study, 2003) coupled with a high caloric diet (Hansen, Vilsboll, Bagger, Holst, & Knop, 2010; Hwu et al., 2004; Ingelsson et al., 2009; Nedeltcheva, Kessler, Imperial, & Penev, 2009) is associated with various cardiovascular and metabolic disease. Moreover, sedentary behavior is directly related to insulin resistance (Alibegovic et al., 2010; Amati et al., 2009; Eckardt, Taube, & Eckel, 2011; Hamburg et al., 2007).

In people at risk for Type 2 diabetes, low cardiorespiratory fitness (VO_2max, 22 ± 6 mL· kg· min^{-1}) is a risk factor for development of the disease (Leite et al., 2009). Individuals with Type 2 diabetes with low and moderate fitness levels have risk factors associated with cardiovascular disease and insulin resistance (Kadoglou et al., 2009). A cross sectional analysis done by Leite, et al (2009) and Kadoglou et al (2009) on Type 2 diabetics with low and moderate fitness levels are described as having a cardiometabolic profile associated with low cardiorespiratory fitness (see Table 2). In healthy populations, two weeks of inactivity can significantly impair peripheral insulin sensitivity, and cardiovascular fitness (Olsen, Krogh-Madsen, Thomsen, Booth, & Pedersen, 2008).

Table 2

Characteristics of at Risk and Type 2 Diabetics with Low VO_2max

	Type 2 Diabetics		At Risk
	Low fitness	**Moderate fitness**	
VO_2max (ml/kg/min)	20.0 ±3	23.5 ±3	21.9 ±6
Patients	46	46	369
Men/Women	20/26	20/26	291/78
Duration of diabetes (Yr)	5.4 ±1.6	6 ±2.6	
Age (Yr)	56.9 ±9	58.0 ±7.1	45.7 ±10
BMI (kg/m_2)	31 ±4.6	29.8 ±3.6	28.8 ±6.3
Waist Circumference (cm)	112 ±11.9	10 ±12.5	
Systolic BP (mmHg)	141.7 ±16	125.8 ±	125 ±15
Disatolic BP (mmHg)	89.6 ±9	81.2 ±9	80.0 ±8.4
Antidiabetic Regimen (Sulf, Gl, Met/Combined)	8/2/20/16	6/2/23/15	
Antihypertensive medication	24	21	
Medication (%)	52.2	45.7	
ß-blockers	5	3	
Ace inhibitors	15	11	
Calcium Channel antagonist	3	2	
Lipid-lowering medications	10	13	
Physical Activity (active/total)	5/46(10.9%)	43/46(96.5%)	
Fasting glucose (mg/dl)	190 ±51	170 ±36	
HbA1c (%)	7.8 ±1.9	7.4 ±1.2	5.4 ±0.5
Total cholesterol (mg/dl)	222.6 ±56	214.7 ±3.8	206 ±38.5
HDL (mg/dl)	46.1 ±8.5	51.8 ±8.7	49 ±15
LDL (mg/dl)	144 ±13	145 ±62	128 ±33
Triglycerides (mg/dl)	164 ±74	145 ±62	154 ±90
Uric Acid (mg/dl)	5.4 ±1.36	5.2 ±.96	
hsCRP (mg/dl)	0.49 ±.18	0.31 ±.18	
Fasting insulin (mU/ml)	12.9 ±4.2	10.7 ±3.9	7.2 ±5.1
HOMA-IR	6.76 ±3.8	4.92 ±2.2	1.51 ±1.1

Note Data are means ± S.D. ; SULF, sulfonylureas; GL, glindes; MET, metformin; Combined, sulfonylurea+metformin; FPG, Fasting plasma glucose; HbA1c, glycosylated hemoglobin; hs-CRP, high-sensitivity CRP; HOMA-IR, homeostatic model assessment of insulin resistance. Modified from Kadoglou et al., 2009 and Leite et al., 2009

Bird and Hawley (2012) suggest inactivity associated with an increased prevalence of insulin resistance, Type 2 diabetes, and cardiovascular disease is caused by the disease-susceptible genes coupled with environmental (inactive state) conditions contributes to the "exercise deficient phenotype" (Bird & Hawley, 2012). In support of this hypothesis, novel animal models are developed by creating low (low capacity

runners) and high (high capacity runners) intrinsic aerobic phenotypes (Kivela et al., 2010; Koch et al., 2011). Rats with low capacity running phenotype have diminished skeletal muscle capillarity and mitochondrial area while high capacity runners have higher resting metabolic rate, voluntary activity, serum high density lipoproteins, muscle capillarity, and mitochondrial area (Kivela et al., 2010). Moreover, low capacity runners were heavier and had increased blood glucose, insulin, and triglycerides compared to the high capacity phenotype. Interestingly, when high capacity phenotypes are exposed to a high fat diet (12 weeks), they were protected against obesity and insulin resistance (Noland et al., 2007). Low cardiorespiratory fitness and exercise capacity are strong predictors of all-cause mortality (Kokkinos et al., 2010; Kokkinos et al., 2008). However, exercise can improve these mortality risks (Kokkinos et al., 2010).

Exercise and Insulin Action

Exercise can maintain optimal blood glucose, lipid, and blood pressure profiles, which prevent or delay chronic complications of diabetes (American Diabetes, 2010; Eriksson, 1999; Ostergard et al., 2006; Zanuso et al., 2010). Consistent with those findings, short-term and prolonged exercise programs, at moderate intensities, can improve blood-glucose concentrations (Denton, Schultz, Jamurtas, & Angelopoulos, 2004; Eriksen, Dahl-Petersen, Haugaard, & Dela, 2007; Eriksson, 1999; Zanuso et al., 2010). A classic study (Holloszy, Schultz, Kusnierkiewicz, Hagberg, & Ehsani, 1986) demonstrated that high levels of aerobic exercise training (running 25-35km) at moderate to high intensities significantly improved glucose tolerance and insulin resistance. This

volume of exercise performed on a regular basis was suggested as a requirement to completely normalize glucose tolerance in patients with mild Type 2 diabetes and impaired glucose tolerance (Holloszy et al., 1986). However, moderately high intensity training is unlikely to be performed by patients with Type 2 diabetes; given their prevalence of low exercise capacities (Brassard et al., 2006; Brassard & Poirier, 2009; Broderick, 2006; Eriksson, 1999; Gusso et al., 2008; Kasahara et al., 2006; McAuley, Myers, Abella, Tan, & Froelicher, 2007; Nadeau et al., 2009; Ribisl et al., 2007).

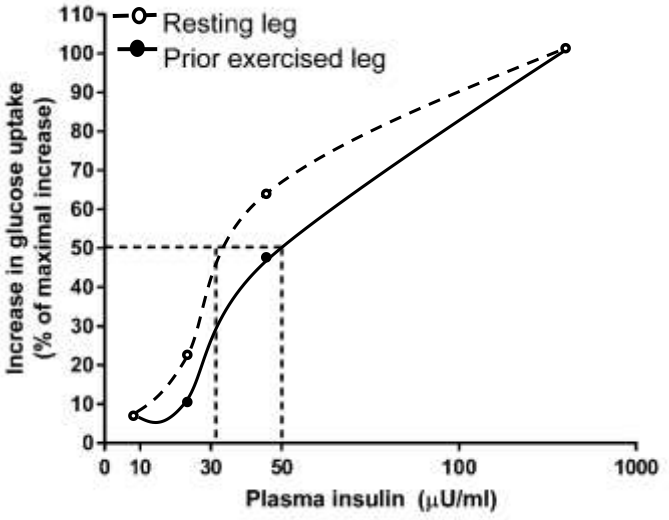

Figure 2. A bout of exercise improves insulin sensitivity of glucose uptake in skeletal muscle of the exercised leg (open circles). A leftward shift of the exercised leg represents a decrease in insulin concentration required to elicit a half maximal glucose uptake compared to non-exercised rested leg (Starkie, Hargreaves, Lambert, Proietto, & Febbraio, 1999; Wojtaszewski, Nielsen, & Richter, 2002).

Insulin sensitivity following a single bout of exercise is improved 2 (Mikines, Farrell, Sonne, Tronier, & Galbo, 1988), 4-6 (Wojtaszewski et al., 2000), 12-16 (Devlin, Hirshman, Horton, & Horton, 1987; O'Gorman et al., 2006), 24, and up to 48 h (Hawley

& Lessard, 2008; Schneider, Amorosa, Khachadurian, & Ruderman, 1984; Zierath, 2002) post exercise, due perhaps to the lasting effect of contracting skeletal muscle on the action of insulin, which increases permeability and signaling of the muscle cell to allow glucose passage (Z. P. Chen et al., 2003; Frosig et al., 2004; Richter et al., 2004) (See figure 2). The precise mechanisms are not well understood; however, muscle contraction leads to an insulin independent effect via activation of AMPK (5' Adenosine Monophosphate-Activated Protein Kinase) that likewise causes the translocation of GLUT4 to the cell membrane as well as increases GLUT4 gene expression (Daugaard et al., 2000; Daugaard & Richter, 2001; Holloszy, 2008; Holmes & Dohm, 2004; Hussey, McGee, Garnham, McConell, & Hargreaves, 2012; Kraniou, Cameron-Smith, & Hargreaves, 2006; Lehnen et al., 2011; O'Gorman et al., 2006; Zisman et al., 2000), thereby improving glucose tolerance and insulin sensitivity (Z. P. Chen et al., 2003; Frosig et al., 2004; Richter et al., 2004). AMPK is a key regulator of skeletal muscle metabolism and gene expression and is believed to be an important signaling molecule for adaptations caused by exercise training (Richter & Hargreaves, 2013; Russell, Foletta, Snow, & Wadley, 2013). Furthermore, exercise is known to have an anti-inflammatory effect by reducing pro-inflammatory cytokines in obese and diabetic humans (Belotto et al., 2010; Gielen et al., 2003; Petersen & Pedersen, 2006; Teixeira de Lemos et al., 2009). Moreover, acute exercise reduces JNK activity and restores insulin sensitivity by modulating IRS (pSER) in humans (Kiraly et al., 2010; Pauli et al., 2010; Teixeira-Lemos, Nunes, Teixeira, & Reis, 2011) rat models (Berdichevsky, Guarente, & Bose,

2010; Kiraly et al., 2010; Ropelle et al., 2006) and in cell cultures (Berdichevsky et al., 2010). HSP72 functions as a natural inhibitory protein of JNK (H. S. Park, Lee, Huh, Seo, & Choi, 2001; Volloch, Gabai, Rits, Force, & Sherman, 2000) and improvements in insulin signaling and glucose uptake in diabetes attribute to limiting inflammatory kinase disruption of insulin signaling (Gabai et al., 1997).

Importantly, exercise increases HSP expression (Banfi, Dolci, Verna, & Corsi, 2004; Naito, Powers, Demirel, & Aoki, 2001; Poso, Eklund-Uusitalo, Hyyppa, & Pirila, 2002; Quindry, 2012; Walsh et al., 2001; Whitham & Fortes, 2008; P. Yamada, Amorim, Moseley, & Schneider, 2008), which may contribute so some of the beneficial effects of exercise on glycemic control. Exercise will increase HSPs in response to a varied stress response such as muscle contraction (Y. Liu & Steinacker, 2001), ischemia (Bushell et al., 2002; Lepore, Hurley, Stewart, Morrison, & Anderson, 2000; Y. Liu et al., 2002), alterations in metabolism (Ndisang, 2013), oxidative stress (Fittipaldi, Dimauro, Mercatelli, & Caporossi, 2013), and glycogen depletion (Febbraio & Koukoulas, 2000; Khassaf et al., 2001). Moreover, the extent of such changes are dependent on training status, intensity, duration, and mode, damaging and non-damaging exercise, and fiber recruitment (Y. Liu & Steinacker, 2001; Morton, Kayani, McArdle, & Drust, 2009). Animal studies have shown that acute exercise increases HSP70 in tissues such as skeletal muscle, lymphocytes, spleen, heart, brain, and liver (Campisi et al., 2003; Lollo, Moura, Morato, & Amaya-Farfan, 2013; Mikami, Sumida, Ishibashi, & Ohta, 2004; Pahlavani, Harris, Moore, Weindruch, & Richardson, 1995; Salo, Donovan, & Davies,

1991; Touchberry et al., 2012). Interestingly, high intensity exercise of short duration raises HSPs as effectively as longer duration exercise and produces similar positive metabolic effects on skeletal muscle (Bartlett et al., 2012). Moreover, resistance exercise, which can cause significant muscle damage, has demonstrated that mammalian target of rapamycine (mTOR) signaling is important for inducing hypertrophy (Apro, Wang, Ponten, Blomstrand, & Sahlin, 2013; Farnfield, Breen, Carey, Garnham, & Cameron-Smith, 2012). Recently, mTOR has been implicated as a key protein for the activation of HSF1 in cell cultures (Chou, Prince, Gong, & Calderwood, 2012). Exercise induced heat shock proteins have been extensively studied in cardiac tissues and are thought to serve a cardio protective role for ischemia reperfusion injury. In fact, a single exercise bout will increase HSP70 in large and small vessels (Milne, Wolff, & Noble, 2012) and myocytes and improve ischemia recovery and reduce infarct size (Dillmann & Mestril, 1995; Mestril, Chi, Sayen, & Dillmann, 1994; Mestril, Chi, Sayen, O'Reilly, & Dillmann, 1994; Nishizawa et al., 1996). Similarly, a cross-tolerance response (Whitley, Goldberg, & Jordan, 1999), such that an exposure to one stress (exercise) can protect against other stresses (i.e. hypoxia and or ischemia) or cross talk (Vigh, Horvath, Maresca, & Harwood, 2007) may also occur in skeletal muscle.

It has been suggested that elevating muscle temperature at rest, comparable to exercise in active men does not elevate HSP in skeletal muscle (Morton et al., 2007). However, others have shown that both the time course and magnitude of HSP expression appears to be associated with baseline HSP levels and that those with lower HSP levels

will respond faster with larger inductions (Khassaf et al., 2001; Morton et al., 2006; Morton et al., 2008; Tupling, Bombardier, Stewart, Vigna, & Aqui, 2007). This has been observed in healthy humans that increase HSP mRNA expression in skeletal muscle immediately after exercise and up to 2 - 3 h post exercise, but do not increase HSP expression levels because basal levels were already elevated (Hernando & Manso, 1997; Puntschart, Vogt, Widmer, Hoppeler, & Billeter, 1996; Walsh et al., 2001). Healthy or trained individuals may need a greater stimulus (ie., exercise intensity or duration) that induces glycogen depletion (Febbraio et al., 2002; Khassaf et al., 2001) or higher intensity that causes muscle damage as observed with resistance exercise (Gjovaag, Vikne, & Dahl, 2006; Khassaf et al., 2001; Paulsen et al., 2007). In contrast to the deconditioned Type 2 diabetic with low basal HSP expression levels, exercise my provide a robust mechanism for inducing HSPs. Additionally, exercise substantially increases energy expenditure by stressing mitochondrial functioning within the skeletal muscle (Gollnick, Armstrong, Saubert, Piehl, & Saltin, 1972; Hamilton & Booth, 2000; Harber et al., 2012), and improves glycemic control (Colberg, 2012).

Thus, exercise which can stress and increase heat shock proteins, can play a major role in enhancing the endogenous defense system against mechanical and metabolic muscle damage, which has the potential for cross talk mechanisms for improving insulin signaling and reducing inflammatory induced insulin resistance.

Heat Shock Proteins

The study of the stress response were first observed and studied by French physiologist Claude Bernard. He first defined this term “milieu interieur” (homeostasis) and Walter Cannon, (American physiologist) who coined the term fight or flight response, (Selye, 1950) were the first to observe this adaptive response. Furthermore, Hans Selye, a pioneer Hungarian endocrinologist, built upon the work of Cannon and Bernard, suggested the physiology of stress has two components, 1) a set response termed “general adaptation syndrome” and 2) the pathological state of unrelieved stress (Selye, 1950). Selye published a review article titled “Stress and the General Adaptation Syndrome,” in which he suggested any stress that causes a danger to life is met with an adaptive response.

Placing stress (psychological or physical) that challenges the homeostatic environment induces adaptive responses, which will strengthen and improve the cell function of the system to cope with further insults. All cells have this mechanism in place through upregulaton of stress proteins commonly termed heat shock proteins (HSPs). Heat shock proteins (HSPs) are highly conserved and provide protection from chronic and acutely stressful conditions that impair cellular homeostasis. HSPs can function as molecular chaperones that aid in a variety of physiological processes in a variety of organisms, tissues, and cells (Chakrabarti, Chen, & Varner, 2011). The heat shock response is known it’s role in facilitating the protein synthesis, assists in secretion,

trafficking, transcription factor removal, and protein kinases (Bukau, Weissman, & Horwich, 2006).

HSPs belong to a multi-gene family and are classified by their molecular size (kilo-Dalton). The 70-kd protein is termed HSP70.The associated gene for HSP70 protein is hsp70 (Whitley et al., 1999). The family of HSPs was originally named "heat shock" proteins because their expression levels increase after heat exposure, however, environmental or metabolic stressors can induce them. These stressors include: ischemia, heavy metal ions, ethanol, psychological and surgical stress, and viral means. (Macario & Conway de Macario, 2005) (see table 3).

Table 3

Cell Stressor that Induce Heat Shock Proteins.

Stressor or Type	**Name or Description**
Physical	Heat (inducing fever), cold, several types of irritation, including ultraviolet light and magnetic fields
Oxygen	Oxygen-derived free radicals (reactive oxygen speceies) hydrogen peroxids, a shift from anaerobiosis to aerobiosis (reperfusion), hypoxia-anocia (ischemia)
pH	Alkalosis, acidosis, pH shifts
Biological	Infection, inflammation, fever
Psychological	Emotions, emotional conflicts, hormonal imbalance (hypothalamic-pituitary-adrenal axis and autonomic nervous system)
Osmotic	Changes in the concentration of salts, sugars, and other osmolytes (hyperosmotic, hypoosmotic shock)
Nutritional	Starvation invovling multiple nutritional components (carbon, glucose, nitrogen, phosphate, and nitrate)
Antibiotics	Puromycin, tetracycline, nalidixic acid, doxorubicon
Metals	Cadmium, copper, chromium, zinc, tin, aluminum, mercury, lead, nickel
Mechanical	Compression, shearing, stretching
Other	Desiccation, benzene and derivatives, phenol and derivatives, teratogens, carcinogens, mutagens, arsenite, asenate, amino acid analogues, nicotine, anesthetics, insecicides, pesticides

Modified from (Macario & Conway de Macario, 2005)

Rapid induction is done through transcription and translation processes. A heat shock transcription factor gene regulates (heat shock factor 1) the production of heat shock proteins (Whitley et al., 1999). A stress initiates the activation of HSF (factor) monomers. The HSF monomers form a trimer by moving from the cytosol to the nucleus. The trimer then attaches to the heat shock gene (DNA). Production of HSP occurs via attachment of trimer, messenger RNA, and leads to transcription. Messenger RNA moves to the cytosol where HSPs are formed (translation). When the ribosome develops polypeptide chains (proteins) within the cell, HSP assists in the correct folding of its operational 3-dimensional configuration. After stress, if proteins become unfolded, heat shock proteins refold or remove damaged or denatured proteins (Whitley et al., 1999).

Activation of HSP from a varied response to stressors increases stress tolerance and cellular protection against harmful exposures that can cause molecular damage. Thus, increasing HSP may offer possible therapeutic benefits for the treatment of disease (Westerheide & Morimoto, 2005). Heat exposure may offer what has been termed "thermo-tolerance." The idea of cross-tolerance, proposed by Whitley et al. (1999), suggests exposure to one stress (hyperthermia) can protect against other stresses (i.e. hypoxia and or ischemia) (Whitley et al., 1999). Furthermore, thermo-tolerance in experimental models protects against cardiac, renal, and hepatic ischemia, arterial injury, endotoxin shock, and skeletal muscle ischemia-reperfusion (Whitley et al., 1999).

Under normal cellular conditions, proteins are correctly folded with the aid of molecular chaperones, foldases, and lectins (Naidoo, 2009). When protein folding cannot

occur, unfolded proteins or aggregates are targeted and processed by the endoplasmic reticulum-associated degradation pathways. If the unfolded or misfolded proteins accumulate, an unfolded protein response (UPR) is induced by eukaryotes. The unfolded response initiates actions of three functions: 1) adaptation, 2) alarm, and 3) apoptosis (Chakrabarti et al., 2011). The first response, adaptation, induces expressions of chaperones for the refolding of proteins. If this process fails, a cellular alarm and apoptosis system is initiated. The down regulation and expression of pro-survival factors (B-cell lymphoma 2 proteins) and removal of the translational block are initiated. During the third response, cells can undergo apoptosis (Castan-Laurell et al., 2012). Accumulation of misfolded proteins has been strongly associated with a number of disease pathologies such as diabetes, myocardial ischemia, cardiac hypertrophy, atherosclerosis, and heat failure (Chakrabarti et al., 2011).

Type 2 Diabetes and Heat Shock Protein Dysregulation

Obesity and diabetes, which are associated with physical inactivity, may be directly linked to a reduced cellular stress response which is altered due to detraining phenomena from sedentary behaviors (Hooper et al., 2014). Moreover, the low grade inflammatory responses associated with obesity and diabetes may further negatively impair the stress response.

Heat shock proteins (HSPs) provide protection from chronic and acutely stressful conditions that would otherwise impair cellular homeostasis. For example, HSPs reduces protein damage and apoptosis, suppress pro-inflammatory cytokines, repair ion channels,

and aid in protein folding (Benjamin & McMillan, 1998). Reduced intracellular heat shock protein in Type 2 diabetic mellitus is associated with insulin resistance animal models of obesity induced diabetes (Bathaie et al., 2010; Burkart et al., 2008; H. W. Chen et al., 1995; Chung et al., 2008; Gupte et al., 2011; Hooper, 2009; Kondo et al., 2012; Najemnikova et al., 2007). Intracellular HSPs are lower in obese Type 2 diabetics compared to healthy controls, and are inversely correlated with insulin resistance in these patients (Bruce et al., 2003; Figueredo et al., 1996; Kavanagh et al., 2009; Kurucz et al., 2002; Rodrigues-Krause et al., 2012).

Evidence for an impaired stress response in diabetes supported by a reduction in the master regulator (Whitley et al., 1999), heat shock factor 1 (HSF-1) gene expression (Kurucz et al., 2002) in Type 2 diabetics (Atalay et al., 2004; Bruce et al., 2003; Figueredo et al., 1996; Kavanagh et al., 2009; Kurucz et al., 2002; McClung et al., 2008; Nakhjavani et al., 2012; Rodrigues-Krause et al., 2012) (see Figure 7) and HSP72 mRNA (Atalay et al., 2004; Bruce et al., 2003; Kurucz et al., 2002; Nakhjavani et al., 2012; Rodrigues-Krause et al., 2012; Tanner et al., 2002). In human studies, a lower intracellular expression of HSP72 in skeletal muscle correlated with insulin resistance in patients with Type 2 diabetes (Kurucz et al., 2002). Furthermore, genetic analysis suggests low HSP may be an environmental phenomenon as well as a genetic defect (Yechoor et al., 2004). In fact, reduced HSPs may be a primary factor resulting in the development of diabetes and accompanying widespread organ damage (Hooper, 1999, 2003, 2009; Hooper & Hooper, 2005).

In continuing the hypothesis of fatty acid accumulation in skeletal muscle, a rise in diacylglycerol synthesis may activate isoforms of protein kinase C, (IKK-beta and JNK), which phosphorylates key serine residue on the IRS-1. This process disrupts the activation of the insulin receptor on the tyrosine residue and inhibits the signal from being sent further downstream. HSP 27 and HSP 72 have the potential to blunt these negative actions (McCarty, 2006). Obesity-driven inflammation stimulates insulin resistance, which reduces expression of HSPs and increases harmful protein aggregates. Furthermore, the reduction in cellular protection of HSPs results in damage to the pancreatic beta cell which further disrupts insulin signaling and increases inflammation (Atalay et al., 2004; Bruce et al., 2003; Figueredo et al., 1996; Kavanagh et al., 2009; Kurucz et al., 2002; McClung et al., 2008; Nakhjavani et al., 2012; Rodrigues-Krause et al., 2012). If low HSPs are associated with impaired insulin signaling, increasing HSP can offer therapeutic advantages to diseased populations.

Recent studies on obesity-induced insulin resistance supports an inter-regulatory relationship between low HSP72, elevated JNK and serine hyper-phosphorylation and impaired insulin signaling (Chung et al., 2008; Gupte, Bomhoff, Swerdlow, et al., 2009; Gupte et al., 2011; Kondo et al., 2012) (see Figure 3). Specifically, obesity increases free fatty acids and inflammatory cytokines that over activate serine kinase (via JNK and IKK-β), which also blocks HSF-1, impairing HSPs cell protection response (see figure 1 and 2). Conversely, if HSP72 expression was elevated, this would inhibit JNK and thus permit normal cell signaling. The end result is improved glucose tolerance and insulin

sensitivity in obese Type 2 diabetics. HSPs can be induced via pharmacological interventions (Kurthy et al., 2002; Vigh et al., 2007; Vigh et al., 1997), exercise (Banfi et al., 2004; Naito et al., 2001; Poso et al., 2002; Quindry, 2012; Walsh et al., 2001; Whitham & Fortes, 2008; P. Yamada et al., 2008), and heat stress (Bruce et al., 2003; Figueredo et al., 1996; Kavanagh et al., 2009; Kurucz et al., 2002; Rodrigues-Krause et al., 2012), each of which improves insulin sensitivity and glucose tolerance. Given these findings, increasing the induction of HSPs may be a viable approach to improve glycemic control in susceptible populations, as proposed by others (Bathaie et al., 2010; Bruce et al., 2003; H. W. Chen et al., 1999; Chung et al., 2008; Geiger & Gupte, 2011; Gupte, Bomhoff, Morris, et al., 2009; Gupte, Bomhoff, Swerdlow, et al., 2009; Gupte et al., 2011; Hooper, 1999, 2003, 2009; Hooper & Hooper, 2005; Kavanagh et al., 2011; Kurucz et al., 2002; Rodrigues-Krause et al., 2012).

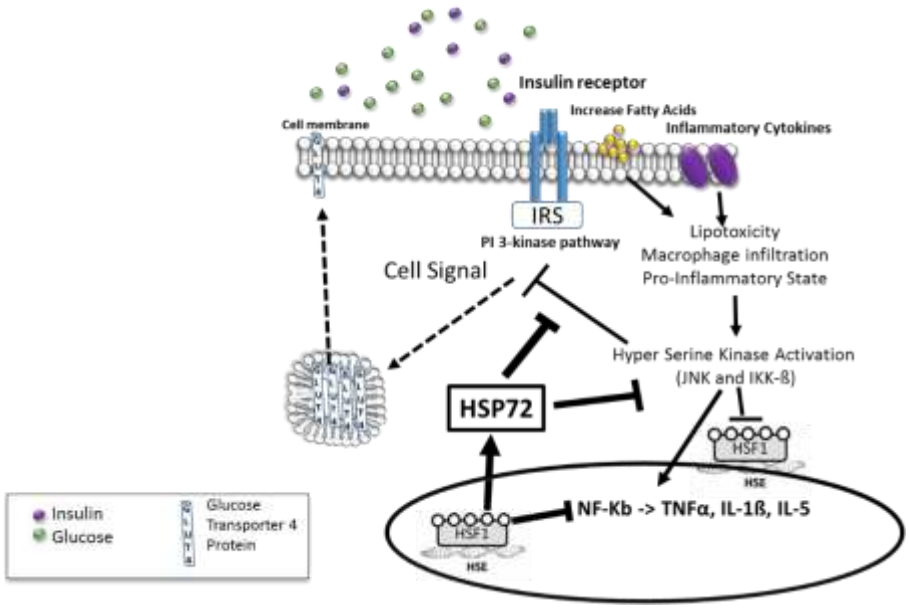

Figure 3. Hypothesized mechanisms in which HSP can inhibit serine kinase activation (Asea & Pedersen)

A Cell Membrane Stress Sensor

Mammalian cells, when exposed to temperatures greater than 37°C (98.6°F), can experience dysfunction. Humans have the ability to tolerate and adapt to a range of environments and rely on physiological responses of sweating, shivering, and alterations of blood flow to maintain thermo-homeostasis. Death often occurs when core body temperature falls below 27°C (80.6°F) or exceeds 42°C (107.6°F) (Keim, Guisto, & Sullivan, 2002). Molecular effects of hyperthermia induce changes in fluidity/stability of the cell membrane and cytoskeleton. This alteration also contribute to apoptosis, impairment of protein function and synthesis, nucleic acids, altered DNA conformation and RNA/DNA synthesis, and other intracellular metabolism, gene expression, and signal transduction processes (Hildebrandt et al., 2002). Cells must therefore have protective mechanisms that sense critical temperatures. Changes in the lipid bilayer of the cell membrane that is exposed to different environmental stress conditions trigger the stress response associated with upregulation of HSPs (Horvath, Multhoff, Sonnleitner, & Vigh, 2008; Vigh, Maresca, & Harwood, 1998). This has led to the "membrane sensor" hypothesis that suggest that protein denaturation or alternation in nucleic acid conformation, and or the physical state of the cell membrane, sstimulate the activation of heat shock genes (Balogh et al., 2011; Gombos et al., 2011; Horvath et al., 2008; Vigh et al., 1998) (See figure 3). Gombos et al. (2011), using the Laurdan two-photon microscopy, fluorescent polarization and electron paramagnetic resonance were able to visualize membrane arrangements through the labelling of lipids with probes and show

changes associated with the heat shocked cells (one hr at 42°C). This has led to a novel drug (BGP-15) that may affect the properties of membranes through molecular dynamic stimulations (Vattulainen & Rog, 2011). Hydroxylamine derivative (BGP-15), an HSP inducer, increases HSP72 expression and improves fasting glucose and insulin concentrations in diabetic compared to control mice (Vigh et al., 2007). Another drug designed to increase HSP expression, Bimoclomol, improves diabetic retinopathy, neuropathy, nephropathy, wound healing, cardiac ischemia, and insulin resistance in laboratory diabetic animal models (Kurthy et al., 2002; Vigh et al., 1997). Finally, when benzyl alcohol is a fluidizing agent are exposed to cells, cells respond by increasing HSPs, intracellular calcium, and mitochondria depolarization, without an increase in temperature (Gombos et al., 2011) which supports the independent effect of changes of the cell membrane that are secondary to hyperthermia stress.

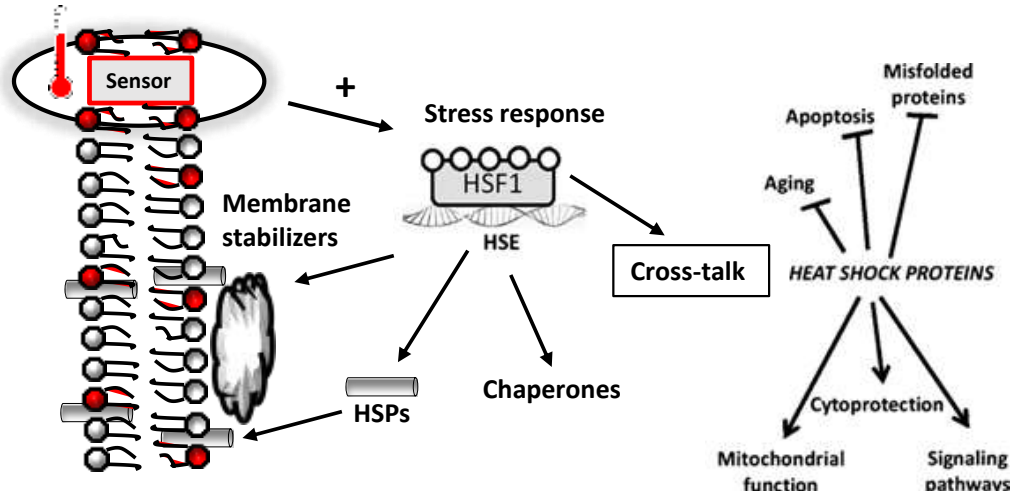

Figure 4. Signal transduction cross talk between altered lipid bilayer and HSP gene expression due to change of physical state and temperature (Gombos et al., 2011).

Heat Shock Proteins and Disease

Critical components of the HSP70 structure are the N-terminal ATP-binding domain (NBD) and a C-terminal substrate-binding domain (SBD) (Broadley & Hartl, 2009). A functional active native state is based on an amino acid sequence, which is a specific three-dimensional structure (Broadley & Hartl, 2009). Avoidance of protein aggregation and attainment of native states is predominantly attributed to molecular chaperones and input of metabolic energy (Broadley & Hartl, 2009). Misfolded or unfolded proteins may occur due to changes in the cellular environment (see above cell membrane sensor). This can be from a variety of cellular environmental stressors, including aging, temperature fluctuations, genetic mutation, or exposure to amino acid analogues (Broadley & Hartl, 2009). Furthermore, an increase in misfolded or unfolded proteins activate the heat shock transcription factors (HSF-1) that increase chaperones via the cytosolic stress pathway, also termed the heat shock response. The immediate expression of genes encoding chaperones are essential for protein homeostasis and minimizes abnormally folded or unfolded species (Broadley & Hartl, 2009; Chiti & Dobson, 2006).

Unchecked protein aggregation and mis-folding are recognized as the root cause of a large and diverse collection of disease known as “protein mis-folding” or “protein conformational disease” (Chiti & Dobson, 2006). Polyglutamine diseases are a family of neurodegenerative conditions that each derive from a CAG triplet repeat expansion in a specific gene that produces a pathogenic protein that contains a critically expanded tract

of glutamines known as prototypical protein misfolding disorders (Shao & Diamond, 2007). Amyotrophic lateral sclerosis (ALS), Alzheimer's, Parkinson's, Huntington's, and other polyglutamine disease occur when non-native conformational proteins aggregate and form in intra and/or extracellular locations (Broadley & Hartl, 2009). It has also been suggested that aggregation of disease proteins may promote inappropriate interactions that are detrimental to the cell and may confer some loss of function which can contribute to disease pathogenesis (Broadley & Hartl, 2009; Chakrabarti et al., 2011; Chiti & Dobson, 2006). Certain diseases, such as Huntington's and Alzheimer's disease, may cause chaperone deficiency, which has been attributed to a continuous decline in the ability to induce the expression of genes encoding chaperones during a stress response, which may be associated by ageing of the human brain (Lu et al., 2004; Rodrigues-Krause et al., 2012).

The heat shock protein families function in co- and post-translational folding and quality control of misfolded proteins (Alexander, Landsman, Teutsch, & Haffner, 2003; Navina et al., 2011). HSP 70 participates in folding and assembly of newly synthesized proteins into macromolecular complexes; aggregation prevention; dissolution and refolding of aggregated proteins; as well as protein degradation (Mayer & Bukau, 2005).

The capacity of the HSP 70 system, and the cellular folding environment, may be overwhelmed by increasing amounts of misfolded disease proteins (Gidalevitz, Ben-Zvi, Ho, Brignull, & Morimoto, 2006). The inability to induce HSP 70 expression above basal levels under stress has been observed in neuronal cells (Kaarniranta et al., 2002;

Marcuccilli, Mathur, Morimoto, & Miller, 1996). As noted earlier this leads to an unfolded protein response (UPR) which induces programmed cell death (Alexander et al., 2003).

Misfolded protein diseases have been strongly associated with a number of other cardiovascular pathologies such as diabetes, myocardial ischemia, cardiac hypertrophy, atherosclerosis, heart failure (Castan-Laurell et al., 2012) and neurodegenerative diseases (K. C. Walls et al., 2012). For example, extracellular Hsp60 have been shown to be associated with risk factors associated with cardiovascular disease (Table 4). HSP60 participates in the folding and assembly of mitochondrial proteins and facilitates proteolytic degradation of misfolded or denatured proteins. Undetectable levels of HSP60 were found to produce 2.03 times higher risk of diabetes mellitus than those with detectable levels after the adjustment for age, BMI, and rate of hypertension (Imatoh et al., 2009). Imatoh et al. (2009) reported an increased expression of human extracellular HSP60 in endothelial cells, macrophages, and smooth muscle cells in human atherosclerotic lesions. Furthermore, Alzheimer disease is associated with mitochondrial dysfunction, and has recently been found that the mechanism leading to amyloid precursor protein and beta-amyloid may be associated with Hsp60 interaction with amyloid precursor protein (K. C. Walls et al., 2012).

Table 4

Relationship Between Circulating HSP60 and HSP70 and Cardiovascular Disease Risk Factors.

Associated with	HSP60	HSP70
Borderline Hypertension	p<.001	x
Diastolc Blood Pressure	r = .34; p <.001	x
24 h Systolic Blood Pressure	r = .179; p = .037	x
Carotid intima-media thickness	p = .009	x
Very Low Density Lipoprotein	p = .017	x
Triglyceride	p < .05	x
Omental Fat, obese vs nonobese*		p < .05

*Adapted from: (Asea & Pedersen, 2010) * (Perez-Perez et al., 2012)*

Skeletal muscle disorders such as Duchenne muscular dystrophy is associated with muscle necrosis and muscle wasting disorders over express HSP 70 in hyper-contracted fibers. These impairments are caused by mutations in the dystrophin gene that result in the absence of the membrane-stabilizing protein dystrophin (Bornman, Polla, Lotz, & Gericke, 1995). Inflammation in dystrophic pathology is well understood. Importantly, it is known that inflammation in this population is due to the pro-inflammatory cytokine tumor necrosis factor-alpha (TNF-alpha) (Porter et al., 2002), which activates nuclear factor kB (NF-kB) and c-Jun N- terminal kinase (JNK) signaling pathways (Monici, Aguennouz, Mazzeo, Messina, & Vita, 2003; Porter et al., 2002). These inflammatory pathways are activated due to the dysregulation of intracellular calcium in dystrophic muscle fibers that are caused by membrane tears, stretch activated channels, calcium leak channels and leaky release channels (Gehrig et al., 2012; Hopf, Turner, & Steinhardt, 2007). In support of the membrane sensor hypothesis, Gehrig et al. (2012) showed increased intramuscular HSP72 by pharmacological inducer (BGP-15) improved the

muscle architecture, strength, and contractile function in dystrophic mice. Furthermore, HSP72 interacts with sarcoplasmic/endoplasmic reticulum calcium ATPase (SERCA) in preserving its function. Importantly, the issues caused by irregularities of the membrane in dystrophic muscle that induce intracellular inflammation may also be associated with obesity induced diabetes and disrupted cell signal transduction.

Insulin deficiency is known to reduce all anabolic processes and increase catabolic processes, regardless of an increase in appetite and food intake. Accelerated protein degradation, mostly in the muscles, provides substrate for gluconeogenesis (Goodman, 2009). HSP expression correlates with muscle oxidative capacity and levels are considerably higher in more oxidative soleus muscle (type I and IIa) compared with the glycolytic (Type IIb) fibers (Gupte, Bomhoff, & Geiger, 2008); (Larkins, Murphy, & Lamb, 2012) (see table 5). Notably, muscle mitochondrial function in diabetes mellitus is likewise impaired by having a fiber type specific defects in the insulin signal transduction to glucose transport (Song et al., 1999). Addtionaly, it is reported that GLUT4 is reduced in slow muscle fibers of Type 2 diabetic patients (Gaster, Staehr, Beck-Nielsen, Schroder, & Handberg, 2001). These fiber type deficits are observed during weight loss. When compared to lean and weight loss intervention groups, the obese had fewer slow twitch fibers. A positive relationship ($r=.72$, $p<.005$) between weight loss and slow twitch fiber was observed (Tanner et al., 2002). Thus, if Type 2 diabetics have reduced amount of oxidative fibers, due to an increase in weight gain, as well as impaired oxidative fibers, this may also suggest a reduced capacity of HSP expressions.

Table 5

Skeletal Muscle Fibers and HSP Content

Muscle Type	Primary Metabolic Pathway	Muscle Contractile Properties	Fatigue Resistance	Mito-chondrial Density	Capillary Density	HSF-1 Expression	Basal Hsp Expression
Type Ia	Oxidative	Slow	High	High	High	High	High
TypeIIa	Oxidative/ Glycolytic	Intermediate	Moderate	Moderate	Moderate	Moderate	Moderate
TypeIIx/d	Oxidative/ Glycolytic	Intermediate	Moderate	Moderate	Moderate	Moderate	Moderate
Type IIb	Glycolytic	Fast	Low	Low	Low	Low	Low

Adapted from (Asea & Pedersen, 2010)

Decreased heat shock proteins (HSPs) in Type 1 and 2 diabetics may be the primary factor leading to the development of diabetes and subsequent widespread organ damage (Hooper, 1999, 2009). The pancreatic β-cells utilize the unfolded protein response signaling to meet the repeated demands of altered levels of insulin synthesis (Chakrabarti et al., 2011). Type 1 diabetes is associated with loss of β-cells and Type 2 with β-cell dysfunction. It is suggested that the overwhelming load on the endoplasmic reticulum (ER) because of insulin production, in response to an increase in blood glucose levels, can negatively impact the folding capacity of the ER, which causes cell stress. This response causes an activation of PKR-like endoplasmic reticulum kinase (PERK) that reduces protein synthesis (Chakrabarti et al., 2011). If the unfolded protein response does not function properly, an increase in unfolded proteins (ie, proinsulin) occurs and causes cell death. This has been supported in PERK -/- cells and PERK deficient mice that show an increase to diabetes and progressive hyperglycemia (Harding et al., 2001). Moreover, in Type 2 diabetes, ER stress causes insulin signaling impairment via JNK-

induced phosphorylation of insulin receptor substrate 1 at Serine residue (Ozcan et al., 2004).

Exercise Mimetics

Exercise, diet, and medication are the primary recommended treatments for diabetes (ACSM/ADA guidelines). Furthermore, due to the potential harmful side effects of drugs (Diamond et al., 2007; Hlatky & Bravata, 2007a, 2007b; Ogihara et al., 2010), therapeutic education on the importance of exercise and diet are more so important. The most recent recommendations for Type 2 diabetes were proposed by the American Diabetes Association and American College of Sports Medicine were to provide evidence for obtaining the maximal benefit of exercise with minimal risk and goals of achieving and maintaining optimal blood glucose, lipid, and blood pressure levels to prevent and delay chronic complications of diabetes (American Diabetes, 2012). In populations at risk for diabetes, strong evidence of increasing physical activity and long term weight loss reduces the risk of developing or delaying the complications of Type 2 diabetes (2009Knowler et al., 2002; Lindstrom et al., 2006; Okada et al., 2010; Shinji, Shigeru, Ryusei, Mitsuru, & Shigehiro, 2007; Um, Lee, Lee, & Kim, 2008).

ADA statement:

"Among individuals at high risk for developing Type 2 diabetes, structured programs that emphasize lifestyle changes that include moderate weight loss (7% body weight) and regular physical activity (150 min/week), with dietary strategies including

reduced calories and reduced intake of dietary fat, can reduce the risk of developing diabetes and are therefore recommended" (American Diabetes, 2012).

Exercise offers great potential for improving the complications associated with obesity and diabetes. Acute and chronic exercise induce mechanical and cellular changes that affect metabolism and organ structure. Acute bouts, depending on intensity of exercise, can result in structural damage to tissues that lead to an adaptive response of tissue repair. Repeated acute bouts lead to enhanced functioning of cardiovascular system and increase mitochondrial function (Gollnick et al., 1972; Hamilton & Booth, 2000; Harber et al., 2012). Additionally, chronic endurance exercise increases skeletal muscle mitochondrial enzyme activity (Dudley, Abraham, & Terjung, 1982; Gollnick et al., 1973; Holloway et al., 2006), respiratory control, and ATP capacity via oxidative phosphorylation (Holloszy, 1967), which improves fatigue resistance (Conlee & Fisher, 1979) by modifying fiber type characteristics (Gollnick et al., 1973). Endocrine adaptions include insulin sensitivity and an increase in muscle glycogen content (Manabe et al., 2012) and fatty acid oxidation, and enzymes of the citric acid cycle (Harber et al., 2012), Furthermore, size and number of mitochondria are responsible for the increase in mitochondrial proteins (Holloszy, 1975). Cardiovascular adaptations include increases in absolute and relative left ventricular mass (Longhurst, Kelly, Gonyea, & Mitchell, 1981; Wernstedt et al., 2002) and vascular density in skeletal muscles (Lash & Bohlen, 1992). Iwasaki et al. (2003) found that training sedentary subjects over a period of 1 year decreased blood pressure, heart rate, and total peripheral resistance, and increased

cardiovascular variability and arterial baroreflex sensitivity similarly as to that observed in competing athletes (Iwasaki, Zhang, Zuckerman, & Levine, 2003). These adaptations would alter both central and peripheral improvements in oxygen transport and utilization (Daussin et al., 2007). Most importantly, similar training adaptations in prediabetics have been observed (Costill et al., 1979).

Several potential exercise related proteins have been proposed to offer similar responses as physical exercise training, such as modulation of the actions in skeletal muscle, of enzymes, transcription factors, transporters and chaperones. These potential targets include 5'AMP-activated protein kinase (AMPK), p38-mitogen-activated protein kinase (MAP), heat shock proteins, peroxisome proliferator-activated recptor (PPAR)-y coactivator-1α (PGC-1α) nuclear factor Kb, GLUT4, fatty acid translocase/CD36, calcium/calmodulin-dependent protein kinase (CAMK)II, certain protein kinase C isoforms, c-Jun N-terminal kiasne, and myokines (Carey & Kingwell, 2009). These proteins that are in direct connection with pathways associated with exercise and mimic the adaptive metabolic responses. However, the majority of studies currently are done in animal models. It has been suggested that of the above list, AMPK, heat shock proteins, PGC-1α, calcium associated signaling and certain MAPKs, are the most likely targets that can mimic the biochemical response to exercise (Carey & Kingwell, 2009). Most importantly, nonpharmacological means for upregulating these proteins may include passive hyperthermia stress (Richter, Kiens, & Wojtaszewski, 2008).

Passive Heat Stress

Passive heat stress may offer similar, benefits comparable to exercise. Mean resting metabolic rate may increase 20 to 40% by heat stress which is associated with an increase in core body temperature (Hasan, Karvonen, & Piironen, 1966). Passive heat stress also improves vascular endothelial function (D. J. Green et al., 2010; Naylor et al., 2011), mitochondria biogenesis (C. T. Liu & Brooks, 2012) and myocardial function (Donnelly et al., 1992; Gowda et al., 1998). 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 remain unclear. In animal models, exposure to high environmental temperatures induces skeletal, structural, and functional changes (i.e. elevated mitochondrial oxidative enzyme activity) (H. W. Chen et al., 1999)) that decreases blood glucose concentrations (Miova, Dinevska-Kjovkarovska, & Mitev, 2008) while increasing insulin concentration (Dervisevik et al., 2011; Kuroshima, Yahata, Doi, & Ohno, 1982). After 28 days of exposure to high temperatures, diabetic rats decreased HbA1c levels and demonstrated improved glycemic control (Domazetobska, 2011). Furthermore, animal models of obesity induced diabetes utilizing repeated heat treatments via warm bath immersion in rats and primates improves glucose tolerance (Chung et al., 2008; Kavanagh et al., 2011; Kondo et al., 2012; Najemnikova et al., 2007; Nakhjavani et al., 2012). Most importantly, in a human study, two weeks of sauna therapy (60°C for 15minutes) altered endothelial function and reduced body weight, blood pressure, and fasting plasma glucose in 25 patients with hypertension,

hypercholesterolemia, and obesity (Biro et al., 2003). Another human study using hot tub therapy (30 mins, three-weeks) significantly decreased fasting plasma glucose and glycosylated hemoglobin levels in patients with Type 2 diabetes (Hooper, 1999).

Repeated bouts of heat stress improve glycemic control in subjects with Type 2 diabetes (Hooper, 1999), in diabetic induced (streptozotocin) mice (Bathaie et al., 2010; Burkart et al., 2008; H. W. Chen et al., 1995; Chung et al., 2008; Kondo et al., 2012; Najemnikova et al., 2007), in genetically induced diabetic mice (Nakhjavani et al., 2012), and diabetic primates (Kavanagh et al., 2011) (see table 6).

Table 6

Hyperthermia Heat Shock Protein Induction Therapies for Diabetes.

Species and metabolic state or model	**Heat or stress applied, intensity, duration frequency**	**Therapeutic result**
Type 2 diabetes patients (Hooper, 1999)	Hot tub: Oral temperature rose 0.8°C, 30 minutes, for 3 weeks, 6 out of 7 days/week	1% fall in HbA1 1.3 mmol/liter, weight loss trend, symptoms of neuropathy improved
Obese subjects (Biro et al., 2003)	Sauna: Rectal temperature rose 1.0°C, 15 minutes at 60°C, daily, 2 weeks	Fasting blood sugar fell 0.3 mmol/liter, weight loss 0.3 kg, BP fell 4mmHg systolic and 5 mmHg diastolic
Obese subjects' ex vivo monocytes (Simar et al., 2004)	Cells incubated for 2 hours at 42°C	Decreases in pJNK, pIKK-β and inhibitory serine IRS-1 phosphorylation
Type 2 diabetes patients (Beever, 2010)	Sauna: far-infrared, 20 minutes, 3 times/week for 3 months	Increased quality of life: reduced stress, fatigue, increased health perception and social functioning
Fat fed mice-- model of t2DM (Chung et al., 2008)	Warming blanket: Rectal temperature 41.5°C for 15 minutes, weekly, 16 weeks	Prevented fat induction of fasting glucose, glucose intolerance, hyperinsulinemia, insulin resistance, and pJNK

Fat fed rats (Gupte, Bomhoff, Swerdlow, et al., 2009)	Hot water immersion: Rectal temperature 41.0°C for 20 minutes, weekly, 3 months	Improved glucose tolerance, insulin-stimulated glucose uptake, increased insulin signaling in slow twitch skeletal muscle, decreased pJNK, pIKK-β, increased mitochondrial enzyme levels
Aged insulin resistant rats 24 months old (Gupte et al., 2011)	Warming blanket: Rectal temperature of 41-41.5°C for 20 minutes, tested 24 hours later	Increase in insulin-stimulated glucose uptake in slow twitch skeletal muscle
Aged insulin resistant rats 24 months old, in vitro soleus muscle (Gupte et al., 2011)	Incubated: 30 minutes at 42°C	Inhibited anisomycin-induced activation of JNK: effect blocked by specific Hsp72 inhibitor
L-6 rat skeletal muscle cell line treated with TNF-α to induce insulin resistance (Gupte et al., 2011)	Incubated: 43°C fro 20 minutes, tested 24 hours later	Preserved ATP-coupled oxygen consumption, and fatty acid oxidation i.e. enhanced mitochondrial function
db/db mice (Kokura et al., 2007)	Far infrared light: Rectal temperature of 38°C for 30 minutes, 3 times/week, 3 months	Improved glycemia, triglycerides, free fatty acid levels, urinary protein excretion, histologic kidney damage, GLUT4 expression
db/db mice and fat mice (Morino et al., 2008)	Heat and mild electric stimulation: 42°C electrodes and 12V direct current (55pps of 0.1 ms duration), 2 times/week for 12-15 weeks	Improved glycemic, reduced insulin levels, reduced liver and body fat, decreased size of adipocytes
HepG2 cells in high glucose medium (Morino-Koga et al., 2013)	Incubation at 42°C and MES for 10 minutes	Increased activating phosphorylation IRS and Akt, increased accumulation of insulin on lipid rafts
db/db mice (Kondo et al., 2012)	Heat and mild electric stimulation: 42°C electrodes and 12V direct current (55pps of 0.1 ms duration), 2 times/week for 12-15 weeks	Reduced beta cell apoptosis and ER stress, increased insulin response to glucose challenge, reduced cytokine activation
Low dose streptozotocin rat (Bathaie et al., 2010)	Hot water immersion: Rectal temperature 41.0°C for 20 minutes, 3 times/week, 5 months	Lowered fasting glucose, Hb A1c AGE, triglycerides, LDL cholesterol, increased HDL cholesterol and insulin secretion

Exercise Combined with Heat Stress Alters Metabolism

Exercise combined with heat stress increases carbohydrate utilization compared to cool environments (Febbraio, Snow, et al., 1994a; Hargreaves et al., 1996; Mittleman et al., 1998), perhaps due to an increase in sympatho-adrenal activity and/or intramuscular temperatures (Jimenez et al., 2007; Radomski et al., 1998). A consistent observation during exercise under heat stress is an increased respiratory exchange ratio (RER) as well as elevated catecholamine concentrations (Febbraio, Snow, Hargreaves, et al., 1994; Febbraio, Snow, Stathis, Hargreaves, & Carey, 1994b; Lee & White, 2004; Mundel, 2008), which suggest that carbohydrate is oxidized at greater rates. During heat stress the hypothalamus, in response to an increased temperature, influences the adrenal glands to increase catecholamines. This has been observed by several researchers showing muscle glycogen use was greater during exercise with heating (Febbraio, Snow, Stathis, Hargreaves, & Carey, 1996; Starkie et al., 1999) (See figure 5). Moreover, blunting the rise in body temperature reduces glycogen utilization, suggesting that heat stress during exercise has a direct effect on carbohydrate metabolism and alters sympatho-adrenal activity secondary to increases in core temperature (Febbraio, Snow, et al., 1996).

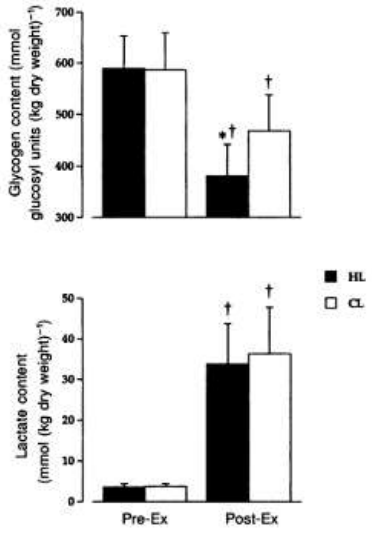

Figure 5. Muscle Glycogen Content Before and After Exercise in Heat. Muscle glycogen content (top) and lactate (bottom) before and after 20min cycle at 70%VO2max with heating limb (HL) or cooling (CL) (Starkie et al., 1999)

The normal resting body core temperature in humans is 37°C. Death often occurs when it falls below 27°C or exceeds 42°C. Humans have the ability to tolerate and adapt to a range of environments and rely on physiological responses of sweating, shivering, and alterations of blood flow to maintain thermo-homeostasis (Brooks, Fahey, & Baldwin, 2005; Cheung, 2010; Greenleaf, 2004). During exercise, human movement is reliant on the ability to convert chemical energy into mechanical energy. However, this metabolic activity is very inefficient. Only about 30% is used for work and 70% of heat production is lost to the environment by radiation, convection, conduction, and vaporization of water (Cheung, 2010). Thus, exercise will increase core body and muscle temperatures in an intensity dependent manner that influences metabolism (Febbraio, Carey, Snow, Stathis, & Hargreaves, 1996; Febbraio, Snow, et al., 1996; Johnson &

Rowell, 1975; Morris, Nevill, Boobis, Macdonald, & Williams, 2005). It is unknown if exercise during heat stress offers a synergistic advantage. However, animal studies (Morino et al., 2008; Nicolai et al., 2009) using electrical stimulation during heat stress during 15 weeks of treatment alters adipose tissue and normalizes glycemic control.

Mechanisms of Exercise and Hyperthermia on Improving Insulin Signaling

Exercise under heat stress may offer additive, or perhaps synergistic, improvements in glucose tolerance relative to either exercise under thermoneutral or passive heat stress conditions. Insulin initiates the movement of glucose transport protein (GLUT4) to the plasma membrane, which allows glucose into the cell (Martin, Slot, & James, 1999; Ploug & Ralston, 2002; Wallberg-Henriksson & Zierath, 2001) as well as increases GLUT4 gene expression (Daugaard et al., 2000; Holloszy, 2008; Holmes & Dohm, 2004; Hussey et al., 2012; Kraniou et al., 2006; Lehnen et al., 2011; O'Gorman et al., 2006; Zisman et al., 2000), thereby improving glucose tolerance and insulin sensitivity. Exercise also increases HSP expression (Banfi et al., 2004; Naito et al., 2001; Poso et al., 2002; Quindry, 2012; Walsh et al., 2001; Whitham & Fortes, 2008; P. Yamada et al., 2008), which may contribute to its beneficial effects on glycemic control (see discussion above). Heat stress may also increases cellular ATP flux rates that activate AMPK (Corton, Gillespie, & Hardie, 1994; C. T. Liu & Brooks, 2012) and Akt (Protein Kinase B) in a temperature dependent manner in rat and human skeletal muscle (Kakigi et al., 2011; Shah, Anthony, Kimball, & Jefferson, 2000; Yoshihara et al., 2013). Heat stress improves insulin sensitivity by increased expression of GLUT4 mRNA in

diabetic mice (Kokura et al., 2007). Notably, GLUT4 proteins are reduced in Type 2 diabetes (Capilla, Diaz, Hou, Planas, & Pessin, 2010; Daugaard & Richter, 2001; Doehner et al., 2010; Gaster et al., 2001; Gaster, Vach, Beck-Nielsen, & Schroder, 2002; Kampmann et al., 2011), thus heat stress alone or combined with exercise may increase GLUT4 expression which will improve insulin and glucose responses. Circulating factors (elevated fatty acids, lipid metabolites, and pro-inflammatory cytokine TNF-α) activate serine kinase IRS activation (via JNK and IKKβ) (Aguirre et al., 2000; Aguirre et al., 2002; Coen et al., 2010; Hooper, 2009; Hulver & Dohm, 2004; Kern et al., 2001; Mishima et al., 2001; Plomgaard et al., 2005; Saghizadeh et al., 1996; Tanti et al., 2004; Yu et al., 2002; Zinman et al., 1999), and disrupts normal downstream cell signaling (Adams et al., 2004; Bachmann et al., 2001; Bruce et al., 2012; Chiu et al., 2013; Jurczak et al., 2012; Powell et al., 2004; Schmitz-Peiffer et al., 1999; Turner et al., 2013). Studies with JNK-1 knockout mice support these conclusions showing decreased serine IRS-1 phosphorylation as well as accompanied marked improvements in insulin sensitivity compared to wild type obese mice (Hirosumi et al., 2002). Thus, inhibition of JNK via exercise or heat stress, by increasing HSP72 (H. S. Park et al., 2001; Volloch et al., 2000) will limit its disruption of insulin signaling (Gabai et al., 1997; Simar, Jacques, & Caillaud, 2012; Volloch et al., 2000). In animal models of obesity induced diabetes, passive heat treatment protected against insulin resistance, decreased JNK activation and IRS serine hyper-phosphorylation (Chung et al., 2008; Gupte, Bomhoff, Swerdlow, et al., 2009; Gupte et al., 2011; Kavanagh et al., 2011; Kondo et al., 2012; Najemnikova et al.,

2007; Nakhjavani et al., 2012). This was further supported by pharmacologically inhibiting HSPs during heat stress, which showed no improvement in glucose tolerance (Chung et al., 2008, Gupte, Bomhoff, Swerdlow, et al., 2009, Gupte et al., 2011).

To date, only one preliminary study investigated the effects of heat "therapy" at rest (via hot-tub immersion) in Type 2 diabetics (Hooper, 1999). Following this therapy, reductions in mean fasting plasma glucose levels (10.1±2.0 to 8.8±2.3 mmol per liter), coupled with a significant reduction (from 11.3±3.1% to 10.3±2.6%) in glycosylated hemoglobin were reported. Despite a number of animal studies demonstrating beneficial effects of heat therapy, no other human trials have investigated the influence of a bout of heat stress, with and without exercise, or the mechanisms of those perturbations in improving glycemic control.

Studies utilizing obesity induced animal models have supported this concept. Heat stress has been shown to induce HSP70 in diabetic induced (streptozotocin) mice (Bathaie et al., 2010; Burkart et al., 2008; H. W. Chen et al., 1995; Chung et al., 2008; Kondo et al., 2012; Najemnikova et al., 2007) genetically induced db/db mice (Nakhjavani et al., 2012) and in diabetic primates (Kavanagh et al., 2011) and humans (Amorim, Yamada, Robergs, Schneider, & Moseley, 2008). Kavanagh et al. (2010) were able to show that restoring HSP70 deficits improved glucose tolerance in diabetic monkeys by heat stress and was further supported by the activation of HSF-1 expression. Grupte (2009) induced HSP72 by heat treatment in high fat-fed rats, which improved glucose tolerance and prevented insulin resistance. Heat treatment decreased

phosphorylation of JNK and IKK-B. Mitochondria function assessed by citrate synthase and cytochrome oxidase activity was lower in the diabetic rats compared to controls; however, heat treatment restored the activities (Gupte, Bomhoff, Swerdlow, et al., 2009; Gupte et al., 2011).

Kondo et al. (2012) investigated whether increasing HSP72 could reduce beta-cell stress signaling, apoptosis and preserve beta-cell mass by utilizing mild electrical stimulation in MIN6 cells and db/db mice. A decrease tumor necrosis factor (TNF)-alpha-induced JNK phosphorylation and reduced endoplasmic reticulum (ER) stress was also observed. In db/db mice, insulin sensitivity was improved following 12 week heat shock treatment. This study suggested increasing HSP70 by heat stress, and mild electrical shock, which mimicked muscle contraction, preserves pancreatic beta-cell volume (Kondo et al., 2012)

Chung et al. (2008) increased HSP72 by three means, exercise, heat stress, and transgenic over expression and resulted in protection against obesity induced hyperglycemia, and hyperinsulinemia. Several inflammatory signaling proteins such as JNK, and IKK-B, and tumor necrosis factor-α induced insulin resistance; however, increasing HSP72 blocked the induction of these molecules (in vitro) (Chung et al., 2008). Whitham and Febbraio (2010) suggest increasing HSP72 as a therapy for the treatment of obesity induced diabetes. In both high-fat diet fed and genetic rat models of obesity, over expression HSP72, heat treatment, genetic and pharmacological manipulation of HSP72 was shown to improve insulin and glucose responses (Chung et

al., 2008). Researchers suggest HSP72 functions as a natural inhibitory protein of JNK (H. S. Park et al., 2001; Volloch et al., 2000) and improvements are attributed to limiting inflammatory kinase disruption of insulin signaling (Gabai et al., 1997). When thermo-tolerance is reduced, HSP72 mediated control of the JNK signaling pathway is also reduced.

In keeping with this hypothesis of heat stress activating HSP and improving insulin sensitivity, heat acclimation (repeated exposure to heat stress) has also been shown to cause alterations in serum enzyme activities in streptozotocin-diabetic rats (Dervisevik et al., 2011). Long-term heat acclimation may lead to alterations of glucose metabolism by changes of glycolysis, as well as tissue damage control of hepatic enzyme activities in STZ-diabetic rats (Domazetobska, 2011). Extracellular heat shock proteins have been studied in normal populations and are associated with a marker of heat acclimation (H. W. Chen et al., 1995; Horowitz & Kodesh, 2010; McClung et al., 2008; P. M. Yamada, Amorim, Moseley, Robergs, & Schneider, 2007). Interestingly those that had a greater increase in heat shock proteins demonstrated the greatest heat acclimation (McClung et al., 2008). Hyperthermia treatment was shown to enhance mitochondrial oxidative enzymes (H. W. Chen et al., 1999) which was associated with an increase in a core body temperature (Amorim et al., 2008; H. C. Chen, Guh, Tsai, & Lai, 1999).

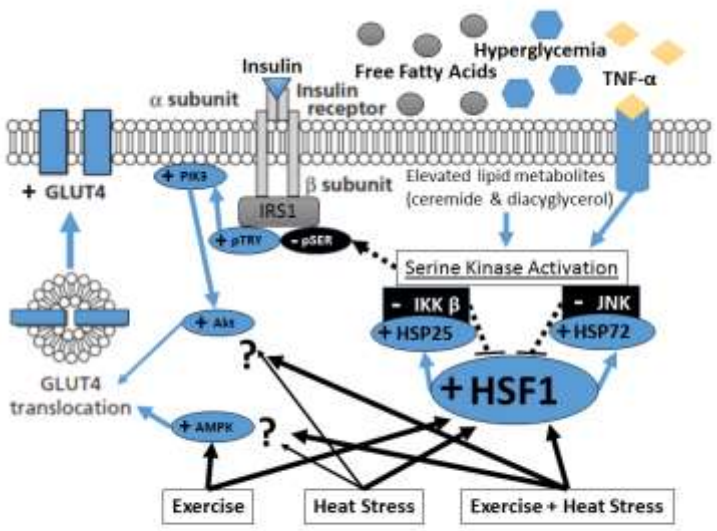

Figure 6. Schematic of proposed mechanisms of improved insulin signaling. Exercise, heat stress, or in combination will block serine kinase activation on IRS1 allowing for normal signaling via IRS1/tyrosine. Exercise and heat stress may also activate Akt or AMPK pathways that increase GLUT 4 expression. Modified from (Gao et al., 2002; Geiger & Gupte, 2011)

Hyperthermia Therapy and Vascular Function

The pathophysiology of Type 2 diabetes is not clearly defined; however, evidence suggests a low grade inflammatory state, coupled with lipotoxicity, impairs normal insulin cell signaling in various organs (Muoio & Newgard, 2008; Schaffer, 2003). Thus, causing peripheral and hepatic insulin resistance (Sheng & Yang, 2008) and impaired pancreatic β-cell function (Alonso-Magdalena et al., 2011) negatively influences blood glucose homeostasis. Moreover, uncontrolled hyperglycemia will cause microvascular and macrovascular complications that will damage vessels leading to atherosclerosis and hypertension that contribute to stroke and cardiovascular disease. Thus, diabetes and hypertension may be interlinked, however the mechanisms are still somewhat uncertain.

Hyperglycemia may impair vascular relaxation by reducing endothelium-derived nitric oxide, (eNO) (Tesfamariam, Brown, & Cohen, 1991; Williams et al., 1998) and elevates hormones, such as endothelin-1, thereby contributing to hypertension (Kolka, Rattigan, Richards, & Clark, 2007), most likely through compromised blood flow. Notably, diabetics and first degree relative of diabetes patients are reported to have increased arterial stiffness, altered nitric oxide release and endothelial function (Ghiadoni et al., 2008; Kimoto et al., 2003; Rerkpattanapipat et al., 2009; Scuteri et al., 2008).

Head out water immersion under thermal neutral conditions (34-35°C) results in cardiovascular, respiratory, renal, and endocrine alterations (Epstein, 1976) in response to hydrostatic pressure and thermoregulatory adjustments (Johansen, Jensen, Pump, & Norsk, 1997). Cardiac output increases (32-62%) in response to redistribution of blood volume (i.e., increase in central blood volume). An increase in stroke volume and a reduction in heart rate occur, while systemic vascular resistance decreases as a constant or slight increase in arterial pressure are observed (Arborelius, Ballidin, Lilja, & Lundgren, 1972; Farhi & Linnarsson, 1977; Pendergast & Lundgren, 2009). However, these responses differ slightly during hot water immersion. An immediate drop in temperature gradient caused by a high thermal conductance will cause the skin and core temperature to rapidly increase. At elevated skin and water temperatures (~39°C), a 112-121% increase in cardiac output have been recorded (Rowell, Brengelmann, & Murray, 1969; Weston, O'Hare, Evans, & Corrall, 1987) with elevations in heart rate, slight increase in stroke volume and reductions in central venous pressure. Moreover, supine

passive thermal stress will increase cutaneous circulation as skin blood flow may increase upwards of 7-8 L/min (Crandall et al., 2008; Minson, Wladkowski, Cardell, Pawelczyk, & Kenney, 1998; Rowell, Brengelmann, Blackmon, Twiss, & Kusumi, 1968). This large redistribution of blood volume is met with adjustments in cardiac output and peripheral adjustments to minimize a reduction in mean arterial pressure. A decreased systolic and diastolic pressure have been previously reported during warm water (36-37°C) immersion (Craig & Dvorak, 1966) and whole body passive heat stress (>1.0°C) via water perfused suit as a result of peripheral vasodilation for heat dissipation (Crandall et al., 2008).

Exercise offers the potential to lower blood pressure profiles. A single bout of exercise can induce post-exercise hypotension, via vasodilation, in sedentary and hypertensive individuals (Halliwill, Buck, Lacewell, & Romero, 2013; M. J. Kenney & Seals, 1993). Most importantly, post-exercise hypotension can have a prolonged effect of up to 13 hrs (M. J. Kenney & Seals, 1993). Passive heat stress may offer similar benefits comparable to exercise by improving vascular endothelial function via sheer stress mechanisms (D. J. Green et al., 2010; Naylor et al., 2011). Most importantly, in a human study, two weeks of sauna therapy (60°C for 15 min) altered endothelial function and reduced body weight, blood pressure, and fasting plasma glucose in obese hypertensive patients (Biro et al., 2003).

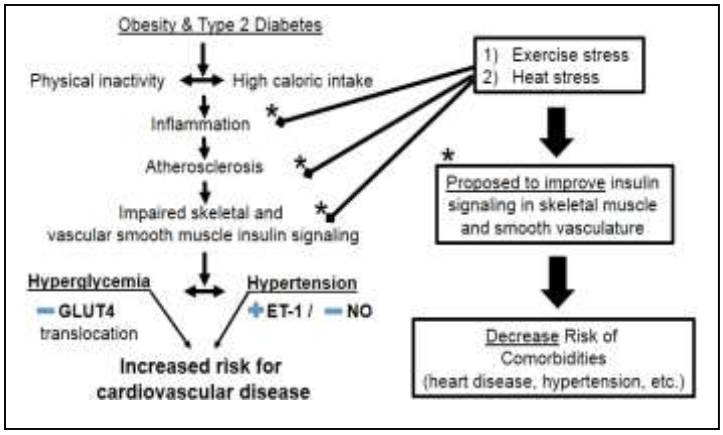

Figure 7. Proposed link between hyperglycemia, hypertension and increased risk of disease. Exercise and heat stress are hypothesized to independently improve (*) these impairments and reduce risk of comorbidities. (**-** = reduced; **+** = elevated)

Cardiovascular and autonomic impairment coupled with altered endothelial function in Type 2 diabetes have been previously reported (Ghiadoni et al., 2008; Kimoto et al., 2003; Rerkpattanapipat et al., 2009; Scuteri et al., 2008; Ziegler et al., 2014). However, passive hyperthermia therapy may offer additional benefits to improving vascular function in obese Type 2 diabetics and hypertensive individuals.

In summary, recent studies of heat shock proteins in obesity related insulin resistance suggest a complex interaction between obesity, inflammation and insulin signal disruption. As the prevalence of metabolic syndrome and associations with the disease increase; more studies suggest that insulin resistance and hyperglycemia are the underlying cause of complications (Eckel et al., 2005; Haffner & Taegtmeyer, 2003). Currently, heat shock proteins are of clinical interest in the pathology of disease, including cancer, neurodegenerative disease, aging, and cardiovascular disease (Gaster et

al., 2001). Research suggests an influential relationship between “stress proteins," commonly termed heat shock proteins (HSPs), and insulin sensitivity (Chung et al., 2008; Gupte et al., 2011; Hooper, 2009) in animal models of obesity induced diabetes (Bathaie et al., 2010; Burkart et al., 2008; H. W. Chen et al., 1995; Chung et al., 2008; Kondo et al., 2012; Najemnikova et al., 2007). Importantly, heat stress may be an effective treatment to improve glycemic control, perhaps secondary to HSP induction. Only one human preliminary study has found, hot water immersion to improve glycemic control in subjects with Type 2 diabetes (Hooper, 1999), while several animal models have found chronic heat stress increased the induction of HSP70 in diabetic induced (streptozotocin) mice (Bathaie et al., 2010; Burkart et al., 2008; H. W. Chen et al., 1995; Chung et al., 2008; Kondo et al., 2012; Najemnikova et al., 2007), genetically induced diabetic mice (Nakhjavani et al., 2012), and diabetic primates (Kavanagh et al., 2011). Moreover, restoring HSP70 deficiencies via heat stress and activation of HSF-1 gene expression improved glucose tolerance in diabetic monkeys (Kavanagh et al., 2011; Zick, 2005). Moreover, Grupte et al. (Gupte, Bomhoff, Swerdlow, et al., 2009; Gupte et al., 2011) induced HSP72 by heat treatment in high fat fed rats, which improved insulin stimulated glucose uptake and insulin signaling, glucose tolerance, and prevented insulin resistance.

Methods of increasing HSF-1 expression can be pharmacological, heat stress, or exercise, which can increase HSPs and provide cellular protection of aging, apoptosis, and misfolded proteins, and improve mitochondrial function and signaling pathways (Asea & Pedersen, 2010). Recent interest has been examined through the induction of

HSPs, in the obese driven insulin resistant animal model and have shown promise in improving insulin sensitivity and blood glucose homeostasis. Determining the biological mechanism of heat shock proteins in improving insulin resistance may result in developing therapies to improve glycemic control and risks associated in disease populations.

CHAPTER III

METHODS

Participants

Nine obese Type 2 diabetic and nine healthy non-obese subjects were recruited for this study. Subjects were not heat acclimated prior to testing. The Type 2 diabetes classification was based on the American Diabetes Association recommendation (fasting plasma glucose ≥126 mg/dL, HbA1C ≥6.5, a 2h 75g glucose tolerance test of ≥ 200) (American Diabetes, 2013). Obesity criteria was based on published guidelines (>39% body fat was considered obese) (Gallagher et al., 2000). All subjects were free of any known chronic illness such as cardiac, neurological, or impaired renal function. Type 1 or Type 2 diabetics that were on insulin, or who smoked were excluded from the study. Females were tested during the early follicular phase of their menstrual cycle. An initial prescreening consisted of obtaining written consent, completing a healthy and physical activity questionnaire, and measures of body composition, height, weight and waist circumference. This study was approved by the Institutional Review Board at Texas Woman's University (see Appendix A).

Research Design

The study is a repeated measures design. Data was collected during seven visits. These visits included one preliminary testing session, two pre-experimental assessments, two experimental sessions, and two post-experimental assessments. The area under the

glucose curve during the OGTT was used to identify statistical power and subject sample size, using the approach of Schutz et al. (I. Park & Schutz, 1999; Potvin & Schutz, 2000) for a two-way repeated measures ANOVA design. To identify at least a 30% difference in glucose responsiveness (i.e. AUC) during the OGTT between any paired trials (effect size 0.8 calculated with data from Mishishita et al. (Michishita, Shono, Kasahara, & Tsuruta, 2008)) a sample size of 8 subjects will result in a power of 0.84, while 10 subjects will result in a power of 0.96, at an alpha=0.05.

Aim 1: Passive Heat Stress Condition Improves Glucose Tolerance and Insulin Responses

Visit 1 (Preliminary Testing Session 1). Informed consent and basic anthropometric measures (height, weight, body composition via Dual-energy X-ray absorptiometry (DXA) scan, and waist circumference) and a blood sample were taken during this time (for hemoglobin A1C and lipid profile). Three days before this visit, participants abstained from alcohol and caffeine consumption. Participants refrained from exercise six days prior to this visit. A food log was recorded 3 days prior to the first OGTT with the goal of repeating the food intake prior to each OGTT thereafter. Subjects were then given their food log and asked to replicate food intake before the next trial. After consuming their last meal, they fasted for a minimum of 12 hrs before arriving to the laboratory, although water intake was allowed. Upon arriving at the lab, a fasting blood sample was obtained followed by an OGTT.

Visits 2 and 4 (Experimental Conditions). Subjects rested for a seated 30 minute baseline and followed a randomization of either a passive heat stress or control rest condition.

The passive heat conditions consisted of instrumentation prior to a 30 minute baseline rest. Participants inserted a temperature sensing rectal probe that provided body temperature throughout the ensuing procedures. Six thermocouples were attached to the participant's skin (chest, shoulder, lower back, abdomen, thigh, calf, and back of neck) to obtain and monitor mean skin temperature. ECG electrodes were placed and monitored heart rate. The participants were also instrumented with an arterial blood pressure cuff (brachial artery). Pre- and post-weight exercise weight was obtained to calculate whole-body sweat loss and monitor hydration status. Water was given ad libitum. Perception of thermal sensation and a physiological strain index was calculated as a measure of psychological and physiological thermal strain.

The control (no heat) condition procedures were the same as during the passive heat condition were replicated with the exception of warm water immersion. Subjects rested in a chair for the same duration of the time.

Visits 3 and 5 (Post-Experimental Conditions). Twenty-four hrs after each experimental condition, having fasted at least 12 hrs after their evening meal, subjects returned to the laboratory to repeat the 2h OGTT. The oral glucose tolerance test followed the guidelines and recommendations of the American Diabetes Association (American College of Sports Medicine., Thompson, Gordon, & Pescatello, 2010). After

fasting blood was taken, participants ingested a standard 75g glucose solution, followed by blood collections at 15, 30, 60, 90, 120 minutes post ingestion. Samples were immediately be placed on ice and subsequently analyzed for glucose, insulin, and C-peptide concentrations at the Texas Woman's University Kinesiology exercise biochemistry laboratory. Area under the curve (AUC) was calculated for plasma concentrations of insulin, glucose, and C-peptide during the OGTT. The primary outcome variables were blood glucose and insulin concentrations during the 2h OGTT.

Aim 2: Passive Heat Stress Induces Acute Reduction in Blood Pressure

Blood pressure was measured intermittently during each condition. Blood pressure measurements were standardized by using the left arm (inclusive of correct cuff size) of all participants with the cuff at heart level. Two to 3 blood pressure measures, with 1 minute interval between, were obtained at 10 min increments during each condition. The primary outcomes for acute blood pressure responses were systolic, diastolic, and mean arterial blood pressure.

Statistical Procedures for Data Analyses

Participant characteristics were analyzed using an independent sample t-test. Changes in body temperature, skin temperature, and thermal perception were analyzed using a repeated measures three way (time x group x condition) analysis of variance (ANOVA). Glucose, insulin, C-peptide, and leptin during each oral glucose tolerance were analyzed utilizing a three way ANOVA. Where appropriate, *post hoc* Bonferroni comparisons were made. Data were analyzed using SPSS Statistics (Version 22, IBM

Corp., Armonk, NY, USA) with significance set at $p \leq 0.05$. All data reported as mean ± SD.

For Aim 1, the main outcome variables for each experimental condition are AUC for glucose, insulin, C-peptide, and leptin during the 2 h OGTT. A one-way repeated measures ANOVA for each AUC was used, followed by a Bonferroni post hoc test.

For Aim 2, the main outcome variables were changes in blood pressure (systolic, diastolic, and mean arterial pressure) during 1 h warm water immersion and post treatment condition. A one-way repeated measures ANOVA for each AUC, followed by a Bonferroni post hoc test was utilized.

Procedures

Instrumentation

For each visit, upon arrival, subjects inserted a rectal thermocouple (Tre; Physiotemp Instruments Inc., Clifton, NJ) ~10 cm past the anal sphincter for the measurement of core body temperature. Mean skin temperature thermocouples (Omega Engineering, Stamfort, CT) were taped (Transpore, 3M Health Care, Neuss, Germany) on the right side of the body and mean skin temperature was calculated using weighted coefficients from six sites. Mean body temperature was calculated by a formula proposed by Burton using coefficients, 0.64 (T_{Core}) + 0.36 (T_{Skin}) (Lenhardt & Sessler, 2006). Heart rate was measured using a standard 12-lead ECG and electrodes (Quinton Q-Stress System, Cardiac Science, Waukesha, WI). Body surface area (BSA, m^2) was calculated according to DuBois and DuBois (Du Bois & Du Bois, 1989) (0.20247 x Height(m)$^{0.725}$ x

Weight(kg)$^{0.425}$). All thermistors were calibrated with a standard thermometer in the warm water bath. Total whole body sweat loss was calculated from pre to post-trial nude body mass (Tanita, Arlington Heights, IL), corrected for fluid intake and urine output.

Passive Heat Stress and Control Condition Procedure

Participants visited the laboratory after 10-12 h fast between 700 and 800 h. After instrumentation, participants 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 (DM2 24.1 ± 1.4°C; HC 23.2 ± 0.6°C; DM2 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 with water temperature set at ~39°C with no differences (P>0.05) between group treatments (DM2 39.4 ± 0.3; HC 39.3 ± 0.4 °C). Subjects rested in this water for 1 h, while temperatures, heart rate, and thermal perceptions were recorded every 10 minutes. Following the 1 h water immersion, the participants were raised, then lowered out of the water into a rested seated position for 1 h. Immediately post immersion participants dried themselves with a towel. Water (500 mL) was provided ad libitum.

Perception and Physiological Strain Index Scales

The perception of thermal sensation scale was measured on a 13 point scale (Dadgar et al., 2010). The physiological strain index, which includes the increase in core temperature and heart rate between pre and end periods (Moran, Shitzer, & Pandolf,

1998) was measured during the duration of both conditions. The physiological strain index is a validated measurement indicating heat strain used primarily during exercising under normothermia and hyperthermia between 36.5-39.5°C. The following formula: 5 (Tret - Tre0) x (39.5 - Tre0) - 1 + 5(HRt - HR0) x (180 - HR0) - 1, where Tret and HRt are simultaneous measurements taken at any time during the exposure and Tre0 and HR0 are the initial measurements.

Body Composition and Anthropometric Measurements

Body composition was assessed by using Dual-energy X-ray absorptiometry (DXA, General Electric, Lunar Prodigy Promo, Madison, WI). Body weight, height, and waist measurement were measured using a standard scale and tape measures. Waist circumference was obtained with participant's arms at their side, feet together and abdomen relax as a horizontal measurement of the narrowest part of the waist above the belly button was recorded.

Blood Collection and Storage

Participants arrived at the laboratory in a fasted (12 hr) state prior to each OGTT. Each participant rested for 30 min prior to the start of each OGTT baseline blood sample collection. Blood collection was performed by a trained phlebotomist and obtained from an indwelling venous catheter. Each blood sample was collected in K_2/EDTA treated vacutainer tube (7 mL) during preliminary session 1, 2, and the days after each condition (OGTT day). Each blood sample was placed in ice water slurry immediately, and then

centrifuge for 10 minutes at 3000 RPM. A pipette was used to remove the plasma and then aliquot in 0.5 mL clean plastic vials, and immediately frozen at -80°C.

Oral Glucose Tolerance Test (OGTT)

Fasting levels of blood glucose and insulin were obtained follow the guidelines and recommendations of the American Diabetes Association (American College of Sports Medicine. et al., 2010; Lorenzo et al., 2010; Sacks, Arnold, Bakris, Bruns, Horvath, Kirkman, Lernmark, Metzger, Nathan, et al., 2011). Participants then ingested a standard 75g glucose solution, followed by blood collections at 15, 30, 60, 90, and 120 minutes post ingestion. All blood measures were centrifuged immediately after was obtained. Plasma was aliquot, then frozen and stored in a -80 °C freezer and subsequently analyzed at the end of study by fluorescent bead-based technology (Luminex multiplex technology). All samples were thawed at the end of the study and subsequently analyzed for glucose (Yellow Springs Instruments Model 2300 Stat Plus Analyzer), insulin, and C-peptide, and leptin concentrations (MAGPIX, Luminex xMAP technology, Milipore, Billerica, MA, USA) in the biochemistry laboratory. This method is comparable in sensitivity to traditional ELISA-based systems but with additional advantages including multiplexing, extended dynamic range, smaller sample size, and dramatically reduced workload. Area under the curve (AUC) was calculated using plasma concentrations for each, insulin, glucose, and c-peptide during the OGTT. All samples were run in duplicates.

Blood Pressure Measurement

Arterial blood pressure measurements were taken using an automated blood pressure instrument (Tango, Suntech Medical) that measured systolic, diastolic, and mean arterial blood pressure. Blood pressure measurements were standardized by using the left arm (inclusive of correct cuff size) of all participants with the cuff at heart level. Two to three blood pressure measures, with 1 minute interval between, were obtained at 10 minute increments during each condition.

Monitoring Dietary Consumption

Each participant recorded all dietary consumption 3 days prior to each condition. This record included all food, beverages, and dietary supplementations that were consumed. Food records were given back to participants to replicate food intake prior to the next glucose tolerance test.

CHAPTER IV

PRESENTATION OF FINDINGS

Participant Characteristics

Nine healthy sedentary and nine obese Type 2 diabetics were recruited for this study. Of the 20 participants, two chose not to complete the study. Both participants withdrew from the study for personal reasons. As presented in Table 7, participant groups were similar in age, height, lean mass, cholesterol, and LDL cholesterol. Because the one goal of the study was to recruit two different groups, participants significantly differed in weight, body surface area, body mass index, fat mass, percent body fat, android fat, hemoglobin A1c, and fasting glucose and insulin values. The Type 2 diabetic group met criteria established by the American Diabetes Association with mean A1C values above 6.5% or fasting glucose ≥ 126 mg/dL and two hr plasma glucose >200 mg/dL (American Diabetes, 2014).

Table 7
Descriptive Characteristics of the Participants

	DM2	HC
Number of subjects (male/female)	9 (3/6)	9 (2/7)
Age (y)	50.1 ± 12.0	41.1 ± 13.7
Weight (kg)	*112.3 ± 26.9	74.0 ± 12.0
Height (cm)	167.8 ± 10	168 ± 8.7
Waist Circumference	*119.6 ± 10.5	89.0 ± 9.6
BSA (m^2)	*2.2 ± 0.29	1.8 ± 0.17
BMI	*40.2 ± 7.4	26.4 ± 3.9
Fat mass (kg)	*55.7 ± 25.3	25.7 ± 9.0
Lean mass (kg)	65.8 ± 19.9	54.5 ± 23.1
Body fat (%)	*45.0 ± 7.1	34.6 ± 7.9
Gynoid Fat (%)	44.1 ± 9.4	38.0 ± 8.7
Android Fat (%)	*52.2 ± 4.8	37.6 ± 9.2
HbA1c (% (mmol/mol))	* 7.5 ± 1.8 (58)	5.3 ± 0.4 (34)
Fasting Glucose (mg/dL)	*151.1 ± 50.1	90.6 ± 10.2
Glucose at 2 h during OGTT (mg/dl)	*266.3 ± 92.5	99.5 ± 33.7
Fasting Insulin (uU/ml)	*15.9 ± 6.2	6.5 ±3.1
Cholesterol	192.6 ± 58.7	168.4 ± 25.1
Triglyceride	*180.9 ± 52.1	73.6 ± 49.6
HDL cholesterol	*36.4 ± 7.6	58.3 ± 14.2
LDL cholesterol	120.1 ± 52.7	96.5 ± 18.8
BMD (m^2)	*1.39 ± 0.2	1.19 ± 0.1

Note. HbA1c, Hemoglobin A1c; BSA, Body surface area; OGTT, Oral glucose tolerance test. * Statistically different from healthy control ($p \leq 0.01$) (mean ± SD).

Thermal Responses during Warm Water Immersion and Control Conditions

As shown in Figure 9, the thermal response to the warm water immersion in comparison to the control condition differed. There were significant differences in core body temperature during both conditions as determined by the three-way ANOVA for time ($F(2.5,40.6) = 106.7$, $p < .001$) and treatment ($F(1,16) = 41.6$, $p < .001$). An interaction effect for time and treatment ($F(2.5,39.9) = 178.4$, $p < .001$) with no effect for treatment x group ($p = .469$) suggests both diabetic and healthy subjects were similarly thermal stressed during the hyperthermia condition. In comparison the control condition,

both groups core body temperature was significantly increased similarly during the hyperthermia condition. Peak core body temperature reached ~38.5°C in both groups during the 1 h warm water immersion condition. These were obviously different than the control day in which core body temperature actually was reduced by .23 °C ($p < .05$) as participants rested over 2.5 hrs. Mean resting core temperature values for the diabetic began at 37.3°C, and significantly reduced to 37.0°C. In the healthy group, baseline rest core temperatures started at 37.0 °C and significantly reduced to 36.8°C at the end of 60 minutes resting during the control condition.

The thermal response during recovery from the water immersion and control conditions are presented in figure 9. There was a significant effect for time ($F(3,48.5) = 87.3$, $p < .001$ and treatment ($F(1,16) = 300.1$, $p < .001$) for recovery core body temperature. A main interactive effect was also found for time and treatment ($F(2.8,45.15) = 156.8$, $p < .001$) with no effect for time and group ($p = .064$). However an interactive time x treatment x group effect was found to be significant ($F(2.8,45.2) = 4.17$, $p = .012$). This may have been a direct effect of significant differences between the group's body mass. These data suggest the obese diabetics' thermal recovery for temperature was attenuated relative to healthy controls. A large mass would take longer to cool after being heated prior.

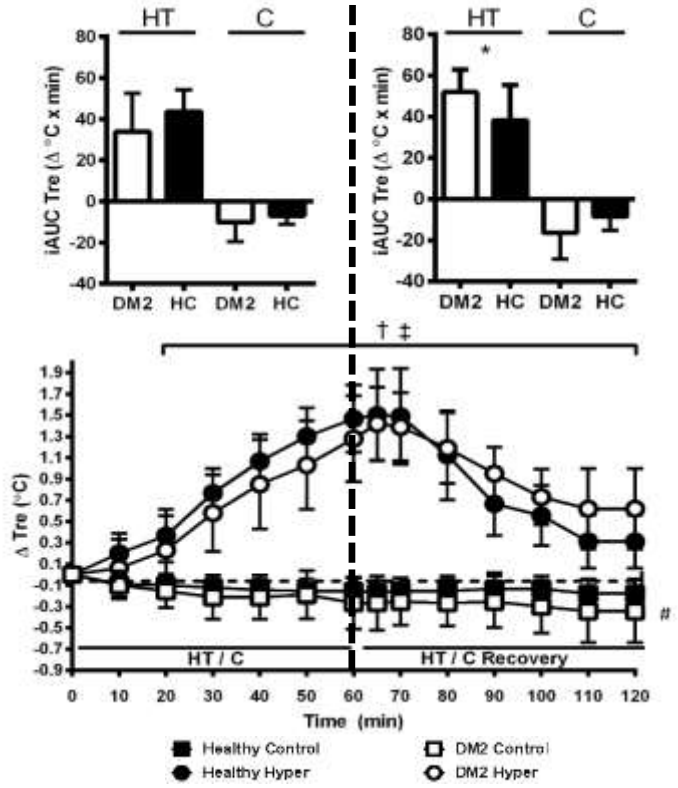

Figure 8. Core Body Temperature. Effect of 60 minutes of hyperthermia, (HT, circle) and control (C, box) treatment on the change (Δ) in core body temperature (Tre). Results are expressed as means ± SD. * Statistically different from control; † Statistically different in control subjects during hyperthermia vs normothermia; ‡ Statistically different in Type 2 diabetics during hyperthermia vs normothermia; # Statistically different from baseline during normotherma. Dashed line represents the end of treatment and start of recovery.

A significant effect for time ($F(32.56,41.04) = 314.8$, $p < .001$) was found for mean skin temperatures during the hyperthermia condition. However, the main effects between groups was not different ($p = .450$). A main effect for condition was reported ($F(1,16) = 633.9$, $p<.001$) with a time x treatment main effect found ($F(2.48,39.62) = 312$, $p<.001$). Both groups similarly increased skin temperature during the hyperthermia warm water immersion condition, and this was different than the control condition. Mean

skin temperature increased by ~6.4°C from resting baseline values (peak mean skin temp 38.2°C) in both groups.

The response for mean skin temperature during recovery are reported in figure 10. A significant effect for time ($F(3.52,56.25) = 51.79$, $p < .001$) was found. No main effects for group or condition were reported ($p > .05$). However, the time x condition effects ($F(2.68, 42.89) = 43.49$, $p < .001$) were significant, which was expected as the warm water increased skin temperature greater than the control condition for both groups.

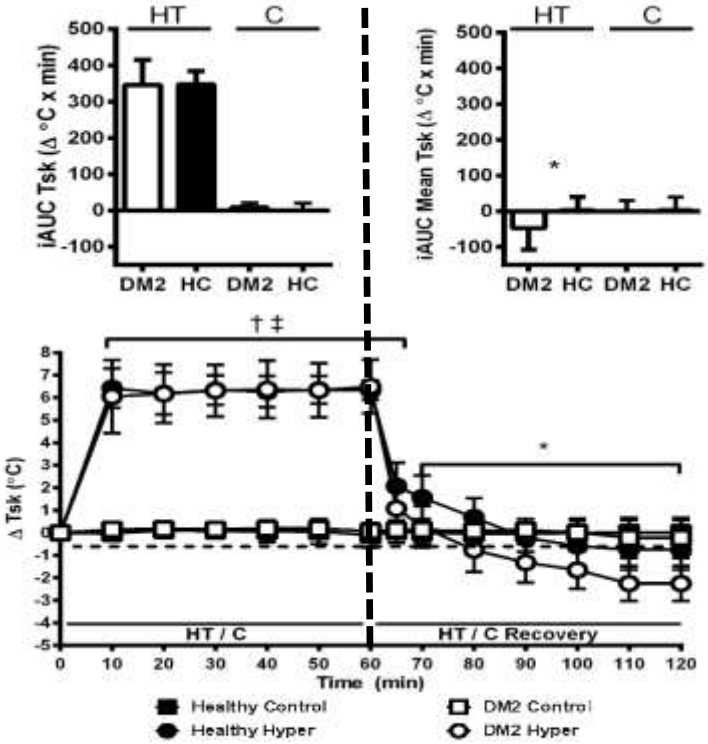

Figure 9. Mean Skin Temperature. Effect of 60 mininutes of hyperthermia, (HT, circle) and control (C, box) treatment on the change (Δ) in mean skin temperature (Tsk). Results are expressed as means ± SD. * Statistically different from control; † Statistically different in control subjects during hyperthermia vs normothermia;
‡ Statistically different in Type 2 diabetics during hyperthermia vs normothermia. Dashed line represents the end of treatment and start of recovery.

Body temperature was significantly elevated during from baseline during the warm water immersion (time, $F(2.4,38.44) = 351$, $p < .001$), with a time x condition interactive effect ($F(2.68,42.9) = 411.19$, $p < .001$). No group differences were reported for body temperature ($p > .05$). Mean body temperature reached $38.4 \pm 0.3°C$ in both groups during the water immersion. Differences in body size did not alter the results during warm water immersion on the change of body temperature (time, $F(2.35, 32.98) = 3.65$ $p = .031$, time x group, $p = .89$).

There were a time effect ($F(3.42,54.78) = 115.24$, $p < .001$) for mean body temperature during recovery. An interactive effect for time and group (time x group, $F(3.42,54.78) = 2.83$, $p = .040$) and condition (time x condition, $F(2.93,46.96) = 116.95$, $p < .001$) during recovery was found. Similar to the differences between body mass, significant difference between groups on body surface area may have influenced these results. Obese individuals have larger surface areas that may have offered more heat dissipation and cooling. However, when body weight (kg) and fat mass (kg) were entered as covariates, no interaction was found (time x kg, $p = .45$, time x fatmass, $p = .50$, time x body surface area, $p = .50$). Thus, when controlling for body mass and surface area, both groups mean skin temperature was reduced at similar rates.

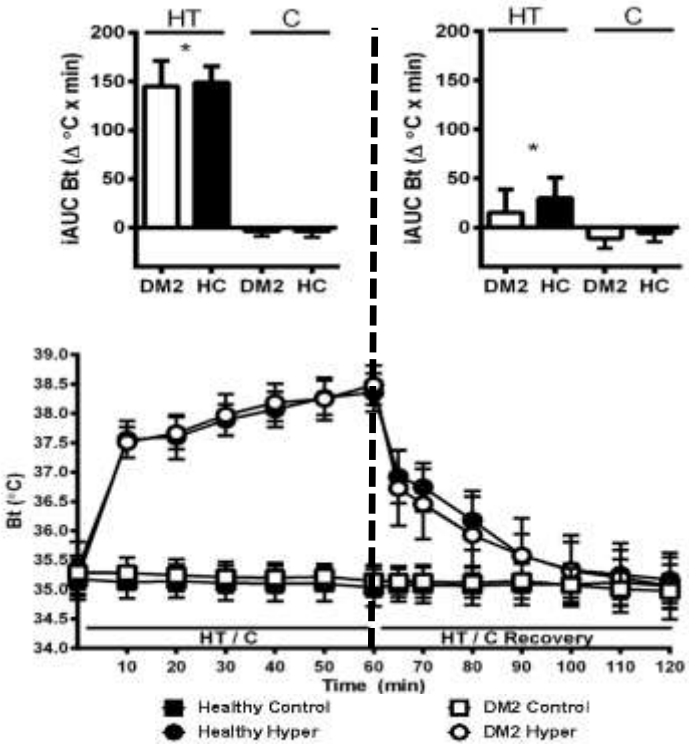

Figure 10. Mean Body Termperature. Effect of 60 minutes of hyperthermia, (HT, circle) and control (C, box) treatment on the change (Δ) in mean body temperature (Bt). Results are expressed as means ± SD. * Statistically different from control. Dashed line represents the end of treatment and start of recovery.

The perception of thermal sensation during warm water immersion showed a significant difference for time ($F(2.81, 44.9) = 33.68$, $p < .001$) with a main interaction with condition (time x condition interaction, ($F(2.87, 45.98) = 33.09$, $p < .001$). No time and group interaction was found ($p = .947$). Moreover, because surface area, body mass and possibly hemoglobin A1C values may influence perception of thermal sensation, when body surface area, body weight, and A1c values are used as covariates, no significant differences were found with these variables as covariates ($p > .05$).

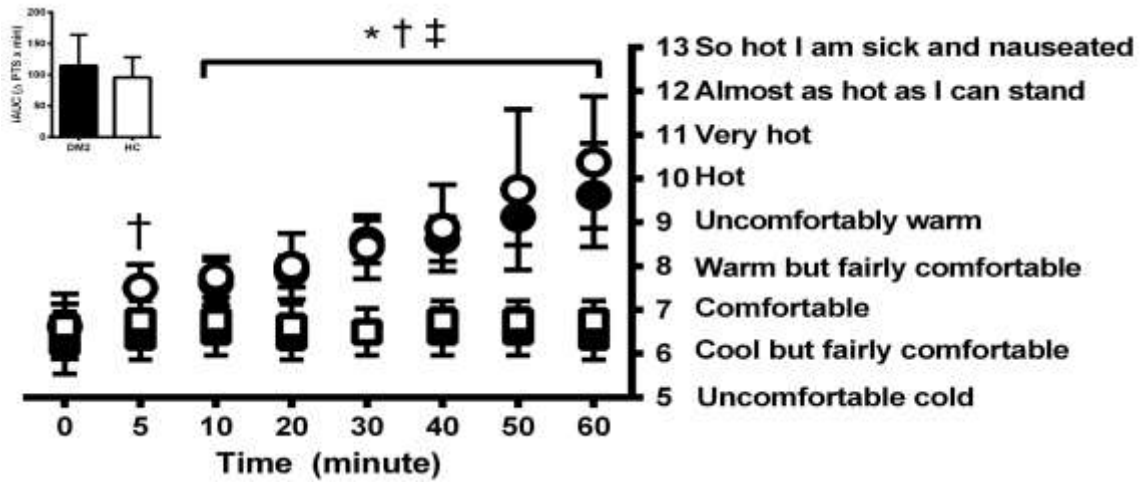

Figure 11. Perception of Thermal Sensation. Effect of 60 minutes (represented by circle) of hyperthermia and control normothermia treatment (box) on the perception of thermal sensation. Results are expressed as means ± SD. † statistically different in control subjects during hyperthermia vs normothermia; ‡ statistically different in Type 2 diabetics during hyperthermia vs normothermia. No group x time interaction perception of thermal sensation (p = 0.947) during hyperthermia treatment day.

Cardiovascular Responses during Warm Water Immersion and Control Conditions

Heart rate significantly increased during the warm water immersion compared to the control condition with significance reported for time and condition (time, $F(3.46,55.46) = 60.19$, $p < .001$, condition, $F(1,16) = 257.6$, $p < .001$). There was a time x condition interactive effect ($F(4.1,65.65) = 81.9$, $p < .001$). No differences between groups were found between conditions (time x group, $p = .944$). Peak heart rate reached 105 ± 10 b/min at the end of warm water immersion.

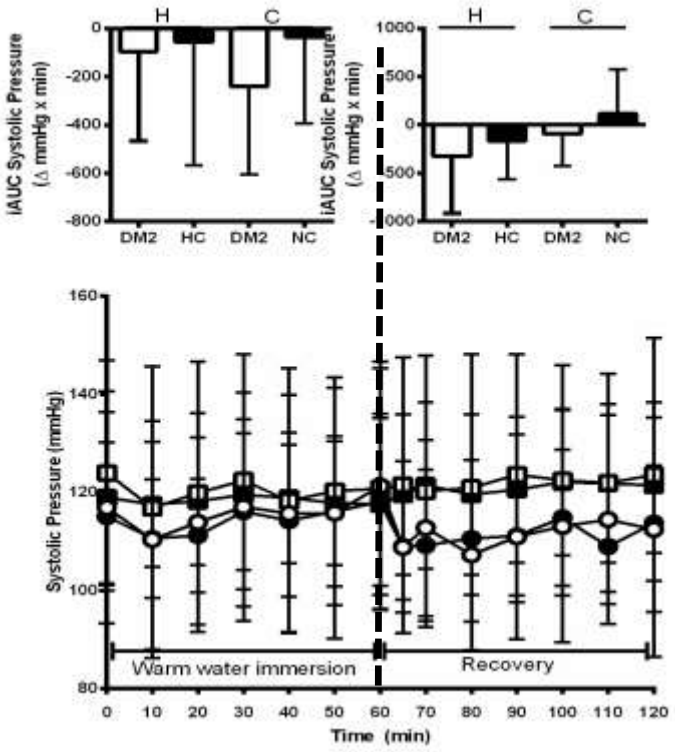

Figure 12. Systolic Blood Pressure. Absolute systolic and delta systolic arterial pressure (and iAUC for each) during a 1h warm water immersion (circle) and control condition (box). Results are expressed as means ± SD. Dashed line represents the end of treatment and start of recovery.

Systolic blood pressure was not changed during either condition (time x group or time x condition interactions, $p > .05$). For systolic blood pressure, a main effect for hyperthermia warm water immersion compared to control condition was found (time x treatment, $F(7,119) = 2.36$, $p = .027$) with no differences between groups (treatment x group, $p = .52$). Diastolic blood pressure during warm water immersion resulted in a reduction over the course of the hr treatment (time, $F(3.28,55.8) = 17.7$, $p < .001$); time x treatment, $F(4.38,74.45) = 22.48$, $p < .001$). No difference between groups was reported (time x group, $p = .776$). Once immersed in warm water, diastolic blood pressure dropped immediately at 5 minutes by 7.2 mmHg and remained lower than pre-immersion

baseline by 12.7 mmHg at 60 minutes. Mean arterial pressure responses during warm water immersion were significantly different than the control condition for time (time x condition interaction, $F(4.38,74.45) = 22.48$, $p < .001$) with no differences between groups (time x group interaction, $p = .776$). Warm water immersion significantly reduced mean arterial pressure as early as 10 minutes (5.4 mmHg) through 60 minutes (10.7 mmHg).

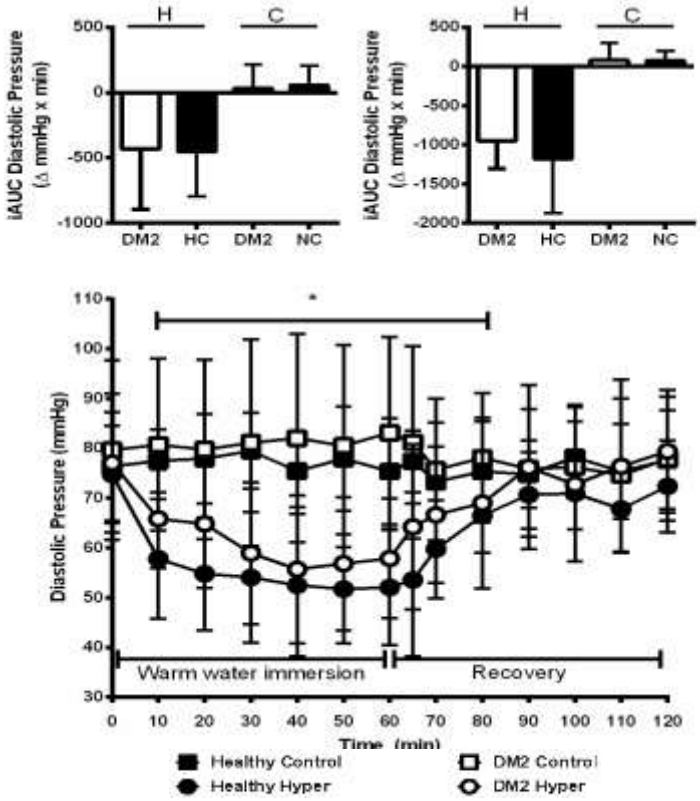

Figure 13. Diastolic Blood Pressure. Absolute diastolic and delta diastolic arterial pressure (and iAUC for each) during the 1 h warm water immersion (circle) and control condition (box) and 1 h recovery for each. Results are expressed as means ± SD. * Significantly different from baseline pre condition, $p \leq 0.01$. Dashed line represents the end of treatment and start of recovery.

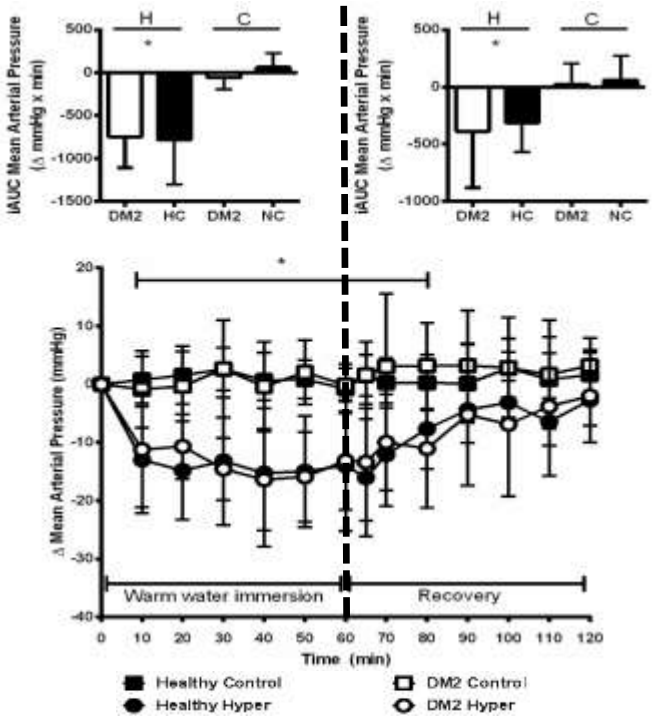

Figure 14. Mean Arterial Pressure. Absolute mean and delta mean arterial pressure (and iAUC for each) during the 1 h warm water immersion (circle) and control condition (box) and 1 h recovery for each. Results are expressed as means ± SD. * Significantly different from baseline pre condition, $p \leq 0.01$. Dashed line represents the end of treatment and start of recovery.

The physiological strain index differed between conditions (time x condition, ($F(3.44,54.97) = 162.6$, $p < .001$). No interactive effect was found between groups ($p = .857$). Physiological strain increased during hyperthermia from minute 20 through minute 60.

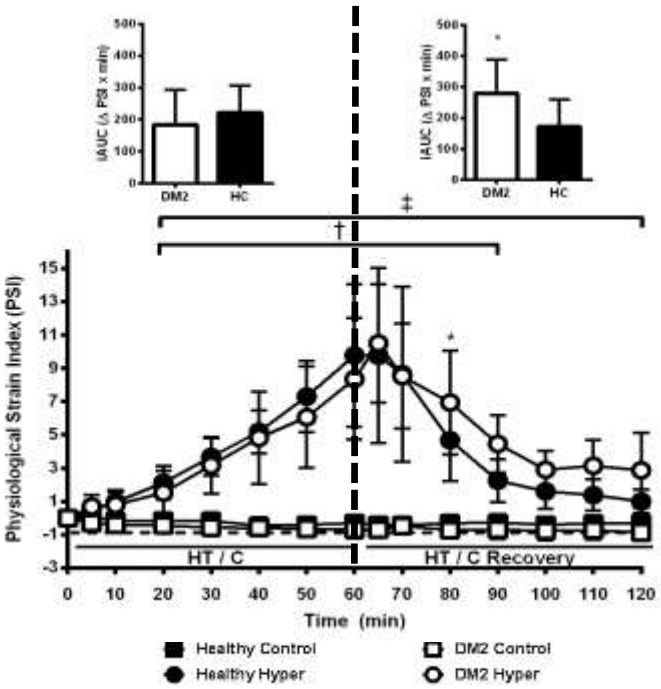

Figure 15. Physiological Strain Index. Effect of 60 minutes of hyperthermia, (HT, circle) and control (C, normothermia) treatment (box) on the change (Δ) in the physiological strain index. Results are expressed as means ± SD.
* Significantly different from control subjects; † different in control subjects during hyperthermia vs normothermia.

Cardiovascular Responses during Recovery from Warm Water Immersion and Control Conditions

Heart rate response during recovery was no different between groups but was different than control conditions (time, $F(3.45, 55.12) = 13.6$, $p < .001$; Time x condition effect, $F(2.89,46.31) = 21.2$, $p < .001$).

During recovery from each condition, no time x group interaction was found for systolic blood pressure ($p = .550$). However, there was a time x condition interaction effect ($F(7,48.4) = 4.01$, $p = .001$) which suggest the hyperthermia condition altered

systolic blood pressure different from the control. Diastolic blood pressure during hyperthermia resulted in a reduction during recovery and in compared to pre-immersion baseline values, diastolic blood pressure remained significantly low at 20 minutes post immersion (6.3 – 4.7 mmHg) ($p<.05$). No differences between groups were reported (time x groups, $p = .217$). A time by condition interaction was found (time x condition, $F(1,17) =13.6$, $p <.001$). An interactive effect for treatment and time was reported during recovery for mean arterial pressure (time x treatment, $F(2.96, 50.28) = 11.75$, $p <.001$) with no differences between groups ($p = .451$). Mean arterial blood pressure was reduced during the hyperthermia condition and differed from the control condition.

The physiological strain index during recovery was not different between groups (time x group, $p =.529$). Main interaction was reported for time and condition (time x condition, $F(2.66, 42.6) =63.95$, $p <.001$). These data suggest that there were no differences with physiological strain between groups during the hyperthermia condition.

Glycemic and Hormonal Response from Warm Water Immersion and Control Conditions

Plasma glucose responses to a 75 g glucose load were different between groups (time x group effect, $F(2.34, 37.38) = 26.49$, $P<.001$). No main effect for condition and time were reported ($p =.114$). The responses for condition were not different ($p = .669$).

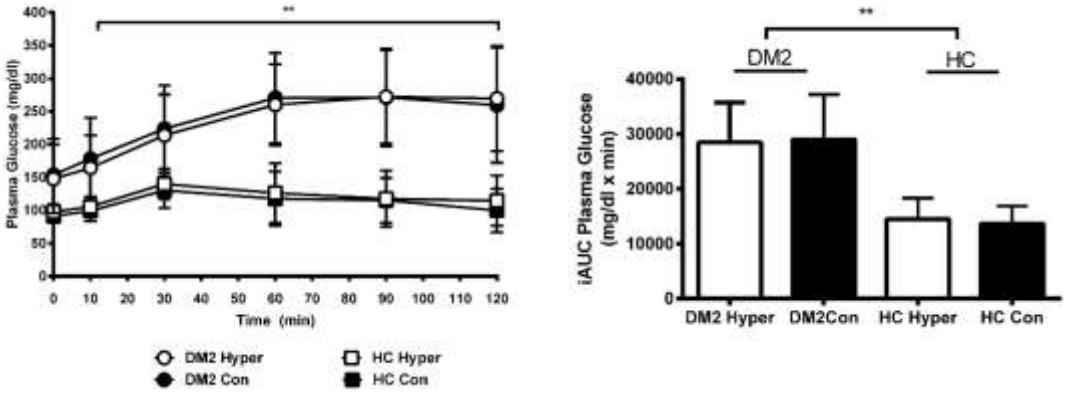

Figure 16. Plasma Glucose and Area Under the Curive. Effect of 60 min (of hyperthermia, (HT, circle) and control (C, normothermia) treatment (box) on glucose responses to the glucose tolerance test. Results are expressed as means ± SD. ** Statistically different from control subjects.

Plasma C-peptide response to a 75 g glucose load were not different between groups (p =.076). An interaction between time and condition was reported (time x condition, F(3.54, 56.6) = 2.7, p = .045). Both groups' insulin values increased over time; however, now there was difference between groups for each condition. Only fasting and 2h time points differed between groups. Plasma insulin responses to a 75 g glucose load were different between groups (time x group, F(2.25, 35.95) = 2.73, p = .025) and no main interaction effect were reported between conditions (condition x group p = .942).

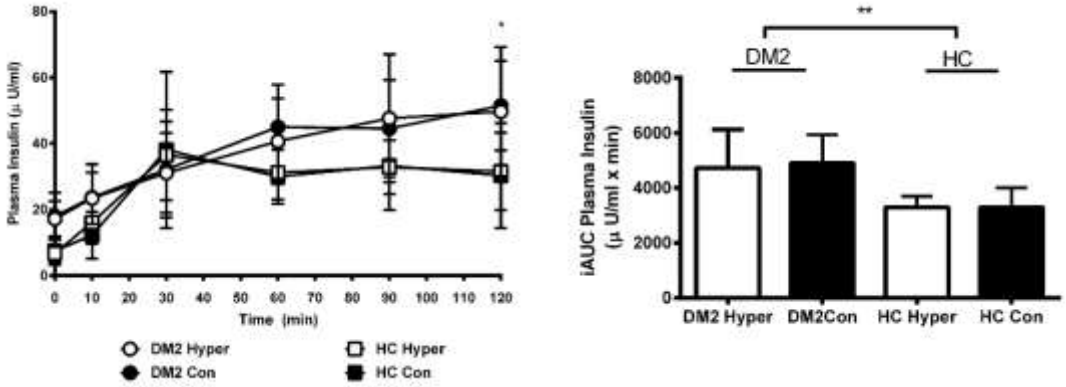

Figure 17. Plasma Insulin and Area Under the Curve. Effect of 60 min (of hyperthermia, (HT, circle) and control (C, normothermia) treatment (box) on insulin responses to the glucose tolerance test. Results are expressed as means ± SD. *, ** Statistically different from control subjects.

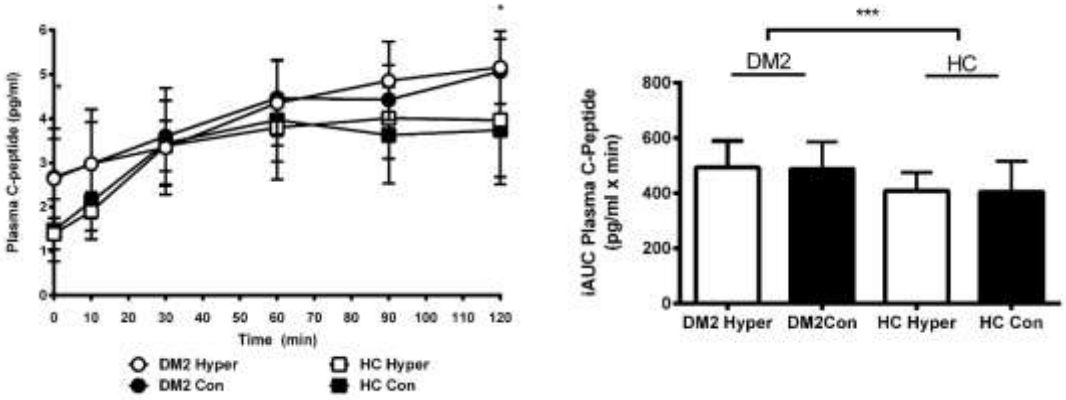

Figure 18. Plasma C-peptide and Area Under the Curve. Effect of 60 minutes of hyperthermia, (HT, circle) and control (C, box) treatment on C-peptide responses to the glucose tolerance test. Results are expressed as means ± SD. *, *** Statistically different from control subjects

Plasma leptin response to a 75 g oral glucose tolerance load showed no significance for time ($F(3.12, 49.86) = 1.78$, $p = .037$) and condition ($F(1,16) = 7.2$, $p = .016$). No main effect were reported for time and group ($p = .125$). All leptin data were combined and compared as means for each condition and group. Mean leptin values

during hyperthermia increased in comparison to control condition (p = .016) for the diabetics. No differences were reported for the healthy control group. When analyzed per kg of fat mass, leptin was significantly elevated for the diabetics group compared to control group (p =.02).

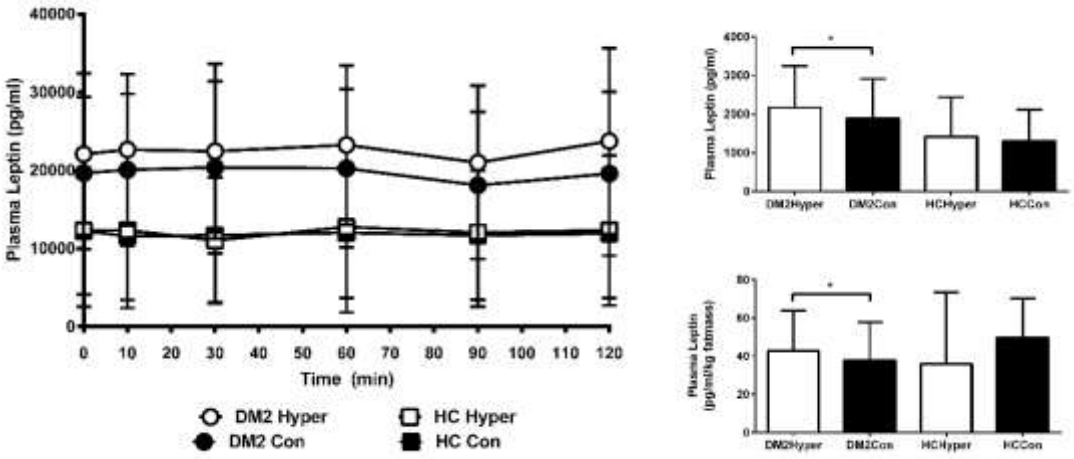

Figure 19. Plasma Leptin and Means. Effect of 60 min (of hyperthermia, (HT, circle) and control (C, box) treatment on leptin responses to the glucose tolerance test. Results are expressed as means ± SD. * Statistically different hyperthermia vs normothermia condition.

No differences were reported for area under the curve during a 75 g glucose load for plasma glucose pre or post hyperthermia and control condition (p = .731). AUC between groups did significantly differ (p < .001). Area under the curve for C-peptide reported no differences for time (pre vs post condition, p = .805) and no main interaction for group (time x group, p = .989). No main interaction effect for time (pre vs. post, p = .562) or group (p = .735) was reported for AUC of insulin. No differences between

groups were reported ($p = .414$). A significant difference was reported for area under the curve for leptin ($F(1,16) = 7.4$, $p = .015$).

CHAPTER V

SUMMARY, DISCUSSION, CONCLUSION, AND RECOMMENTDATIONS FOR FURTHER STUDY

Statement of Problem

The purpose of this study was to determine if a single bout of hyperthermia treatment would improve acute blood pressure responses during and 1 hr post treatment. Additionally, this study aimed to examine the 24h post hyperthermia intervention effect on glycemic and insulin responses to a glucose challenge. Many studies which utilize animal models of obesity induced diabetes in which body temperature was raised by either a single (Gupte et al., 2011) or repeated heat stress treatment (Bathaie et al., 2010; Chung et al., 2008; Gupte, Bomhoff, Swerdlow, et al., 2009; Kavanagh et al., 2011) observe improvements in skeletal muscle insulin signaling and glucose uptake. However, only one reported human study suggested repeated bouts of heat at rest (i.e., 30 min passive heat exposure for 6 days a week for three weeks), via hot-tub immersion, improved markers of glycemic control in Type 2 diabetes. This therapy reduced mean fasting plasma glucose (181.8 ±36.0 to 158.4±41.4 mg/dL) and glycosylated hemoglobin (from 11.3±3.1% to 10.3±2.6%). Thus, passive hyperthermia treatments may offer similar benefits comparable to exercise, and suggest a novel alternative approach for improving diabetic conditions (Hooper et al., 2014). Moreover, repeated passive hyperthermia treatments have also been reported to improve vascular endothelial function

(D. J. Green et al., 2010; Naylor et al., 2011), mitochondria biogenesis (C. T. Liu & Brooks, 2012) and myocardial function (Donnelly et al., 1992; Gowda et al., 1998). Most importantly, other human studies have reported that sauna and hot bath therapy altered endothelial function, reduced body weight, blood pressure, and fasting plasma glucose in obese hypertensive and chronic heart failure and diabetic patients (Biro et al., 2003; Miyata et al., 2008; Shin et al., 2003).

Despite a number of animal studies demonstrating beneficial effect of heat therapy, no human trials have investigated the influence of a single or repeated bout of hyperthermic treatment, or the mechanisms of those perturbations on improving glycemic control or blood pressure responses in obese Type 2 diabetics. Therefore, the present study was performed to investigate if the effect of one acute bout of hyperthermia therapy treatment would improve acute blood pressure responses and alter glucose and insulin metabolism to an oral glucose load.

Characteristics of the Participants

The participants, by design were, obese and Type 2 diabetic and healthy controls. The mean fat mass measured by DXA for the diabetic group was 57.3 ± 25.6 kg which was significantly ($p < .001$) greater than the healthy control group (25.6 ± 9.0 kg). In addition to greater fat mass, body mass (kg, $p < .001$) BMI ($p < .001$), waist circumference (cm, $p < .001$), android fat (kg, $p < .001$) and body surface area (M^2, $p \leq .01$), were all significantly greater in the obese Type 2 diabetics group compared to the healthy control group. Hemoglobin A1C values were 7.5 ± 1.7%, significantly ($p < .001$)

greater than the healthy control group (5.3 ±.3%). All diabetics in the study were previously diagnosed by their medical physician taking medication to control their glycemia. None were prescribed insulin therapy. However, one individual in the Type 2 diabetic group had insulin values similar to healthy control but had the poorest glycemic control (HbA1C, 11.8%) and elevated fasting glucose values (254 mg/dL), that suggests that he should have been on insulin therapy. The mean fasting glucose value for the diabetic group was 147.7 ± 52.1 vs. 97.7 ± 11.6 mg/dL for the healthy group. The 2 h plasma glucose values for the diabetic group was 269.6 ± 79.9 vs.114.6 ±37.9 mg/dl for the healthy group. These mean values for HbA1C, fasting plasma and 2h plasma glucose were directly in line with the American Diabetes Association criteria with mean A1C values above 6.5% or fasting glucose >126 mg/dL or two hr plasma glucose >200 mg/dL (American Diabetes, 2014).

Thermal Changes from Warm Water Immersion

To our knowledge, this study was the first to examine the effect of an acute bout of hyperthermia therapy via warm water immersion on glycemic and acute blood pressure control in an obese Type 2 diabetic population. In healthy non-obese individuals, head out water immersion under thermal neutral conditions 34-35°C) results in cardiovascular, respiratory, renal, and endocrine adjustments, (Epstein, 1976) in response to hydrostatic pressure and the adjustments associated with whole body thermoregulation (Johansen et al., 1997). Cardiac output increases (32-62%) in response to redistribution of blood volume (i.e., increase in central blood volume). An increase in stroke volume and a

reduction in heart rate occur, while systemic vascular resistance decreases as a constant or slight increase in arterial pressure are observed (Arborelius et al., 1972; Farhi & Linnarsson, 1977; Pendergast & Lundgren, 2009). However, these responses differ slightly during hot water immersion. An immediate drop in temperature gradient caused by a high thermal conductance will cause the skin and core temperature to rapidly increase. At elevated skin and water temperatures (~39°C), a 112-121% increase in cardiac output has been recorded (Rowell et al., 1969; Weston et al., 1987) with elevations in heart rate, an increase in stroke volume and reductions in central venous pressure. Moreover, supine passive thermal stress will increase cutaneous circulation as skin blood flow may increase upwards of 7-8 L/min (Crandall et al., 2008; Minson et al., 1998; Rowell et al., 1968). This large redistribution of blood volume is met with adjustments in cardiac output and peripheral adjustments to minimize altered mean arterial pressure. A reduction in systolic and diastolic pressure have been previously observed during warm water (36-37°C) immersion (Craig & Dvorak, 1966) and whole body heat stress (>1.0°C) via water perfused suit as a result of peripheral vasodilation for heat dissipation (Crandall et al., 2008). Thus, the arterial blood pressure adjustments occur secondary to the regulation of body temperature.

We showed no differences among groups (no main interaction) on each thermal variable. Both groups were similarly thermal stressed across the 1 hr of warm water immersion, with no differences ($p < 0.05$) in peak core (DM2, 38.5 ± 0.2; HC, 38.5 ±

0.3°C), peak mean skin (DM2, 38.4 ± 0.6; HC, 38.0 ± 0.6°C) and peak mean body temperatures (DM2, 38.5 ± 0.3; HC, 38.4 ± 0.4°C) during the hyperthermic treatment.

A concern with either exercising or exposure of individuals to hyperthermic conditions is increased potential 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 (Christenson, Geiger, & Anderson, 2013; Semenza et al., 1996). During heat waves hospitalization and emergency department visits increase with diagnosis of diabetes, electrolyte imbalance, and cardiovascular diseases (Basu, Pearson, Malig, Broadwin, & Green, 2012; Bouchama et al., 2007; Knowlton et al., 2009). Moreover, obese individuals that exercise in a hot environment are at greater risk for exertional heat illness (Bedno et al., 2010; Gardner et al., 1996; W. L. Kenney, 1985) possibly due to the storage of more heat compared to non-obese individuals (Yardley, Stapleton, Sigal, & Kenny, 2013). Thus, the potential to utilize warm water immersion as a treatment may include risks of heat related injury.

Patients with diabetes have impaired nocturnal thermoregulation and sensory nerve abnormalities that may impair thermal sensations (Chao et al., 2007; Shun et al., 2004). Moreover, nerve conduction studies report abnormal functional impairments in sudomotor denervation (Luo, Chao, Hsieh, Lue, & Hsieh, 2012; Shun et al., 2004) and are correlated with fasting blood glucose levels and hemoglobin A1C levels. The skin is an important organ for thermoregulatory functions, such as altering cutaneous blood flow, maintaining core body temperature homeostasis (Shibasaki & Crandall, 2010;

Wingo et al., 2010), and perceiving heat stress via thermoreceptors (B. G. Green, 2004). Thus, diabetics have impaired vascular control and vasomotor and sudomotor function, resulting in altered thermoregulation and may be factors that can increase the risk of heat related illness. Most importantly, 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 (Terrien, Perret, & Aujard, 2011).

Both the core and skin temperature are afferent inputs which lead to thermoregulatory alteration to maintain core body temperature homeostasis. The deep core temperature is the main control variable working as a feedback signal (Romanovsky, 2007), while the skin works as a feedforward signal (Werner, 2010). The skin is the largest sensory organ that assist in maintaining body temperature by sensing thermal disturbances and triggering defense responses such as altering vasomotor tone and cutaneous skin blood flow (Savage & Brengelmann, 1996; Shibasaki & Crandall, 2010; Wingo et al., 2010). Core body temperatures are reported to be mostly warmth sensors and trigger autonomic responses important for warmth defense responses that carry a higher influence than skin temperatures (Frank, Raja, Bulcao, & Goldstein, 1999; Romanovsky, 2007; Sakurada, Shido, Fujikake, & Nagasaka, 1993). Additionally, it is suggested that in healthy humans, the relative contribution to thermal comfort is about 1:1 (50 core, 50% mean skin temperature) and between 6:1 and 20:1 for sweating responses (Frank et al., 1999). This suggest the relative contribution of the core thermoreceptors contribute to sweating response during heat stress. Additionally, diabetes

is associated with autonomic dysfunction and prolonged uncontrolled glycemia which can lead to autonomic neuropathy (Gerritsen et al., 2001). Our diabetic group with moderate metabolic control were not clinically diagnosed with neuropathy. In the present study, no differences were found between groups for perception of thermal sensation and physiological strain. This suggests that the water temperatures used in this study were safe and no potential impairments of diabetes disease influenced perception to sensation or thermal strain. The design of the study may be a contributing factor to these results, due to the uncompensable heat stress environment (an inability to dissipate heat during whole body heat stress). It is unknown if these results would be the same in a compensable heat stress environment.

The recovery from hyperthermia differed between the obese diabetic and healthy sedentary individuals when core and skin temperature were expressed as a change from baseline. Others have reported that Type 2 diabetics have impaired skin blood flow and sweating response (Shun et al., 2004; Yardley et al., 2013); however the diabetic group did not differ in sweat rate to healthy controls when expressed as absolute whole body sweat rate or relative per body surface area. We also report that when given the opportunity to drink fluid ad libitum, the diabetic group did not differ from healthy controls ($p = 0.11$, see data in appendix). Surprisingly, however, the diabetic group had higher absolute core temperatures that did not return to baseline values like the healthy control group and their mean skin temperature was significantly lower than healthy control. However, when we normalized to kilogram of body mass, the healthy individuals

had an attenuated reduction of mean body temperature to a greater extent than obese Type 2 diabetics. Regardless of analysis, if absolute core body temperatures reach elevated levels, measures such as fan and/or ice cooling should be considered as a means to reduce body temperatures post hyperthermia.

In summary no difference was found in the responses to a 1 hr bout of thermal stress on skin and body temperatures, perception of thermal sensation and thermal strain between healthy and diabetics. These data suggest diabetic individuals adjust their cardiovascular, thermal strain, and perception to thermal stress in a similar manner as healthy individuals and carried no greater risk to heat related illness as it pertains to the perception of heat stress. Clearly, further research examining chronic hyperthermia treatments in poorly controlled diabetics and those with diagnosed autonomic dysfunction are needed if the benefits of hyperthermia therapy can be translated from animal models to obese and diabetic humans.

Cardiovascular Responses to Passive Hyperthermia

Passive heat stress may offer similar cardiovascular benefits comparable to exercise. Heat stress stresses the cardiovascular system by increasing heart rate, stroke volume and cardiac output for the purpose of redistributing blood from the core to the skin. The redistribution of blood from core to the skin allows for heat dissipation. The increase in blood flow increases sheer stress and improves vascular endothelial function (D. J. Green et al., 2010; Naylor et al., 2011). Others have also reported using hot water immersion in various populations such as healthy (Becker, 2009; Nagasawa et al., 2001)

and people with treated hypertension (Shin et al., 2003), chronic heart failure (Gruner Svealv et al., 2009), coronary arterial disease (Allison, Miller, Squires, & Gau, 1993) and the aged (Ueno et al., 2005). Most importantly, in a human study, two weeks of dry sauna therapy (60°C for 15 min) altered endothelial function and reduced body weight, blood pressure, and fasting plasma glucose in obese hypertensive patients (Biro et al., 2003). Warm water immersion therapy (34°C water temperature, 2/wk for 8 wks) resulted in improvements in ejection fraction and cardiac output, reduced mean arterial pressure and improved quality of life in chronic heart failure patients (Cider, Svealv, Tang, Schaufelberger, & Andersson, 2006; Gruner Svealv et al., 2009).

In the present study, cardiovascular responses to thermal stress were similar in both groups (no interaction effect). Heart rate was elevated up to a peak heart rate of ~105 bpm (DM2, 105 ± 10; HC, 105 ± 10 bpm). We are not aware of any other study that has induced passive hyperthermia via water immersion in obese Type 2 diabetics and assessed cardiovascular responses. Heat stress that increases heat load places cardiovascular strain for the purpose of redistributing blood flow and volume to the skin for heat loss and via sweating. Elevated body temperature will raise cardiac output 3 liters/min per 1°C increase and heart rate will increase 30 beats per minute per degree increase in internal temperature (el-Sherif, Shahwan, & Sorour, 1970; Faithfull et al., 1984). Thus, passive heat stress will induce changes for thermoregulation and adjustments of the cardiovascular system.

Cardiovascular and autonomic impairment coupled with altered endothelial function in Type 2 diabetes have been previously reported (Ghiadoni et al., 2008; Kimoto et al., 2003; Rerkpattanapipat et al., 2009; Scuteri et al., 2008; Ziegler et al., 2014). It is unknown what influence head out warm water immersion has during or post-exposure on arterial blood pressure in obese Type 2 diabetic humans. This study found no differences between the diabetic and healthy group on systolic, diastolic, and mean arterial pressures. In comparison to pre-immersion values, there was no interactive effect for mean arterial blood pressure (MAP, time x group; $p=0.145$). In both groups MAP was reduced ($p<0.01$) from minute 10 (ΔMAP, T2D: 10.2 ± 5.5, HC: 14.8 ± 8.4) through minute 60 of immersion (T2D: 12.8 ± 8.1, HC: 13.9 ± 11.2) and remained below pre-immersion values ($p=0.004$) up to 20 minutes post immersion (T2D: 10.8 ± 9.6, HC 7.6 ± 6.8 mmHg). These data indicate that passive hyperthermia therapy results in similar hypotensive responses between groups.

It has been suggested that shear stress mediates endothelial and arterial wall adaptations to exercise (Markos, Ruane O'Hora, & Noble, 2013; Thijssen et al., 2011; Tinken et al., 2010). Additionally, it has been observed that lower limb exercise, which causes whole body sheer stress, enhances vascular function in non-exercising upper limbs. These studies have utilized a novel design of partially occluding one limb which resulted in an attenuated response compared to the non-cuffed arm (Birk et al., 2012). This work was followed by isolating the increase in blood flow, independent of exercise, by immersing forearms to heating (42°C, for 3 sessions of 30m min for 8wks) using one

arm as a control and a pressure cuff semi-occluding sheer stress design. The alternate arm increased endothelium dependent vasodilation, identifying an independent role for sheer stress on improving vascular function (Thijssen et al., 2011). Thus, passive heat stress may offer a therapeutic benefit to both healthy and diabetic populations. Moreover, repeated passive heat stress has been reported to improve exercise tolerance and endothelial function in other disease populations (chronic obstructive pulmonary and cardiomyopathy, and chronic heart failure patients) (Kikuchi, Shiozawa, Takata, Ashida, & Mitsunobu, 2014; Ohori et al., 2012).

In summary, cardiovascular responses to an acute bout to warm water immersion resulted in similar hypotensive responses in diabetic and healthy individuals. The result of increasing body temperature over 1 hr resulted in a reductions in diastolic and mean arterial pressure during the bout and 20 minutes post immersion.

Glycemic and Hormonal Responses to a 75 g Oral Glucose Tolerance Test Post Warm Water Immersion

Diabetes is the fifth leading risk factor for global deaths and affects 25.8 million people (8.3 % of the U.S. population) (Sacks, Arnold, Bakris, Bruns, Horvath, Kirkman, Lernmark, Metzger, & Nathan, 2011), making it the seventh leading cause of death in the United States. Uncontrolled hyperglycemia subsequently damages vascular and kidney function (Sakallioglu et al., 2007; Triplitt, 2012) which increases the risk for heart attack, stroke, end-stage renal disease and blindness (Alwakeel et al., 2009). While exercise is beneficial (American Diabetes, 2010; Eriksson, 1999; Ostergard et al., 2006; Zanuso et

al., 2010), obese Type 2 diabetics (T2D) have very low exercise capacities (Kadoglou et al., 2009; Leite et al., 2009). Exercise is beneficial in maintaining optimal blood glucose, lipid, and blood pressure profiles, which prevent or delay chronic complication of diabetes. Moreover, insulin sensitivity following an acute bout of exercise is improved up to 48 h post exercise (Hawley & Lessard, 2008; Schneider et al., 1984; Zierath, 2002), due perhaps to the lasting effect of contracting skeletal muscle on the action of insulin, increasing the translocation of GLUT 4 protein to the plasma membrane. (Z. P. Chen et al., 2003; Frosig et al., 2004; Richter et al., 2004).

It is well established in animal models of obesity induced diabetes, that acute and chronic hyperthermic treatments improve insulin signaling and glucose uptake. It is hypothesized that through increasing tissue temperature will improve insulin signaling by inhibiting the negative effect of inflammatory pathways on the insulin receptor substrate. A reduced basal and stress heat shock response (HSPs) is suggested to be a primary factor resulting in the development of diabetes and accompanying widespread organ damage (Hooper, 1999, 2003, 2009; Hooper & Hooper, 2005). Heat shock proteins provide protection from chronic and acutely stressful conditions that would otherwise impair cellular homeostasis. A strong relationship exists between HSPs and insulin resistance (Chung et al., 2008; Gupte et al., 2011; Hooper, 2009) in animal models of obesity induced diabetes (Bathaie et al., 2010; Burkart et al., 2008; H. W. Chen et al., 1995; Chung et al., 2008; Kondo et al., 2012; Najemnikova et al., 2007).

In humans, it is reported that intracellular HSPs are lower in Type 2 diabetics compared to healthy controls, and are inversely correlated with insulin resistance in these patients (Bruce et al., 2003; Figueredo et al., 1996; Kavanagh et al., 2009; Kurucz et al., 2002; Rodrigues-Krause et al., 2012). This is further supported by a reduction of heat shock factor 1 (HSF-1), which is the master regulator gene that expresses HSPs (Kurucz et al., 2002; Whitley et al., 1999), in Type 2 diabetics (Atalay et al., 2004; Bruce et al., 2003; Kurucz et al., 2002; McClung et al., 2008; Nakhjavani et al., 2012; Rodrigues-Krause et al., 2012). Thus, by increasing the temperature of tissues, upregulating heat shock proteins may improve glucose uptake.

This study investigated an acute bout of passive hyperthermia treatment on glucose and insulin responses to an oral glucose tolerance test. The results of the study revealed that an acute 1 hr bout of increasing body temperature in both healthy and Type 2 diabetics did not improve glucose or insulin responses 24 hours post hyperthermia condition.

This study did not directly measure intracellular or extracellular heat shock proteins, however, it is possible that the hyperthermia treatment was not sufficient to elicit a response. The cell culture and animal literature suggest increasing tissues for at least 15 minutes at temperatures up to 41-42°C (see table 6). The water temperature in the present study was set at 39.4 ± 0.4°C and mean core body temperatures for both groups increased 1.4 ± 0.4° above their baseline values (i.e., 37°C baseline increase to 38.4°C). It is highly unlikely that a treatment similar to the one used in this study could utilize higher

temperature water. The physiological strain index and perception of thermal sensation scale utilized in this study suggests that both groups were at peak values (physiological strain index, diabetic: 10.1 ±2.5, healthy: 9.1 ±2; perception of thermal sensation, diabetic: 10.5 ±1, heathy: 9.8 ±1) at the end of 60 minutes. However, it may be possible to utilize a higher temperature for a shorter duration, or use only local hyperthermia treatments in large muscle groups (i.e., higher temperatures with only half body immersion) to replicate the positive results of the animal work. To our knowledge, this is the first study to utilize this approach using warm water immersion while testing glycemic response post treatment in obese diabetic humans.

Interestingly, mean leptin levels during the glucose tolerance test were significantly elevated 24hr post warm water immersion compared to the control condition. Leptin is a long term regulator of energy balance and suppresses food intake, which further impacts body weight (Klok, Jakobsdottir, & Drent, 2007). This may improve insulin sensitivity (Ross, 2003; Ryan et al., 2014) by utilizing repeated bouts of hyperthermia stress and altering appetite hormones and eating behaviors.

Only one study in mice has suggested the relationship between hyperthermia treatments on changes of appetite hormones and eating behaviors. Morera et al., recently reported that when mice were exposed to heat stress continually (5 consecutive days at 45°C) utilizing an infrared ceramic heat lamp, and in comparison to the control condition, blood glucose an fatty acids were decreased. Additionally, leptin, adiponectin, their receptors, and insulin receptor substrate-1 and glucose transporter mRNAs were

upregulated (Morera, Basirico, Hosoda, & Bernabucci, 2012). Another study, in cell cultured 3T3-L1 adipocytes similarly heat stressed (41°C) resulted in elevations in leptin secretion and mRNA in a temperature dependent manner (41°C compared to 39°C) (Bernabucci et al., 2009). The decreased appetite and leptin response to heat stress have previously been reported in research on livestock. In dairy cows, circulating adipokines, and reduced feeding in response to heat stress are suggested to play a role in reduced body weight (Gentry et al., 2002; Sanchez, McGuire, & Beede, 1994). Clearly more work in humans should investigate the influence of heat stress as a modality to reduced food intake, which will have an indirect influence on improving insulin sensitivity and glycemic control by reducing body weight and adiposity (Ross, 2003; Ryan et al., 2014).

Recommendations for Further Study

Based on the observations in the study, an acute 1 h bout of hyperthermia therapy at ~39.5°C water temperature does not improve glycemic control or insulin responses. However, one bout did alter leptin responses 24 h post immersion during the glucose tolerance test, which may change eating behaviors associated with obesity and diabetes over a longer period. Given that the majority of animal studies that report improvements of insulin sensitivity have used higher stress temperature up to 42°C, other studies should examine repeated bouts or local hyperthermia at higher temperatures. We reported that the physiological strain index and perception of thermal sensation are similar in Type 2 diabetics with moderate metabolic control as healthy individuals. This suggests diabetics with moderate glycemic control can perceive thermal strain similar to healthy individuals

and carry no greater risk of heat related illness as it related to thermal sensation. However; the hyperthermia treatment utilized in this study increase passive cardiovascular and thermal strain to peak values. Thus a modified designed study that can use higher temperatures should be researched either by local hyperthermia or partial immersion and shorter durations.

We also report that acute hyperthermia reduced blood pressure similarly in moderate controlled Type 2 diabetics and healthy individuals. Further research into utilizing chronic bouts of warm water immersion hyperthermia may improve endothelial function via a sheer stress mechanism and offer benefits similar to exercise (i.e., post-exercise hypotension). However, this should be verified. It may be that this therapy done repeatedly may improve vascular function in individuals with hypertensive/or endothelial dysfunction.

The co-existence of hypertension and hyperglycemia are common in Type 2 diabetes (Barzilay et al., 2012; Cooper-DeHoff et al., 2010) and are major risk factors for cardiovascular disease (Selvin et al., 2004; Zhang, Hu, Yuan, & Chen, 2012). According to the Centers for Disease Control and Prevention (2011), heart disease and stroke account for 68% and 16%, respectively, of diabetes related deaths among people 65 years or older. Moreover, adults with diabetes have heart disease and stroke death rates 2 to 4 times higher than non-diabetic populations. Thus, further research on the effect of thermal stress on cardiovascular and metabolic improvements would have broad and immediate clinical relevance. Non-pharmacological therapies such as warm water

immersion could potentially prevent or delay the comorbidities of diabetes such as heart disease, hypertension, and the metabolic syndrome, as well as have a huge impact on the U.S. economic burden (medical cost of up to 174 billion dollars). Furthermore, other similar projects could lead to more mechanistic investigations into understanding the influence of heat stress on insulin signaling in smooth and skeletal muscle. These insights can provide the potential for further investigations regarding the link between hyperglycemia, hypertension, and cardiovascular disease related disorders.

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APPENDIX A

Institutional Review Board Approval Letter

TEXAS WOMAN'S UNIVERSITY
DENTON DALLAS HOUSTON

Institutional Review Board
Office of Research and Sponsored Programs
P.O. Box 425619, Denton, TX 76204-5619
940-898-3378
email: IRB@twu.edu
http://www.twu.edu/irb.html

DATE: July 25, 2014

TO: Mr. Eric Rivas
Department of Kinesiology

FROM: Institutional Review Board - Denton

Re: Extension for Effects of Acute and Chronic Whole Body Heat Therapy on Insulin and Glucose Response in Healthy Individuals and Type 2 Diabetes (Protocol #: 17398)

The request for an extension of your IRB approval for the above referenced study has been reviewed by the TWU Institutional Review Board (IRB) and appears to meet our requirements for the protection of individuals' rights.

If applicable, agency approval letters must be submitted to the IRB upon receipt PRIOR to any data collection at that agency. If subject recruitment is on-going, a copy of the approved consent form with the IRB approval stamp is enclosed. Please use the consent form with the most recent approval date stamp when obtaining consent from your participants. A copy of the signed consent forms must be submitted with the request to close the study file at the completion of the study.

This extension is valid one year from August 2, 2014. Any modifications to this study must be submitted for review to the IRB using the Modification Request Form. Additionally, the IRB must be notified immediately of any unanticipated incidents. All forms are located on the IRB website. If you have any questions, please contact the TWU IRB.

cc. Dr. Charlotte Sanborn, Department of Kinesiology
Dr. Vic Ben-Ezra, Department of Kinesiology
Graduate School

APPENDIX B

Interview Forms

Acute and Chronic Warm Water Immersion Study

PARTICIPANT NAME		**SCREENER:**
HOW DID YOU HEAR ABOUT STUDY?		**DATE:**
AGE (18-60) & YEAR BORN (1950-1992)		**QUALIFY** ☐ Yes ☐ No
PLACE OF BIRTH		**SUB ID #:**
APPROXIMATE HEIGHT		
DATE LAST WEIGHED		
APPROXIMATE WEIGHT		
ETHNICITY	☐ Hispanic ☐ African-American ☐ Caucasian ☐ Other	
MEDICAL CONDITION		
MEDICAL DISABILITY		
MEDICATIONS		
SUPPLEMENTS		
BLOOD DRAWING OKAY	☐ Yes ☐ No	
HIGH BLOOD SUGAR LEVELS	☐ Yes ☐ No	
APPROXIMATE BLOOD SUGAR		DATE LAST MEASURED
PHYSICAL ACTVITY	☐ Yes ☐ No	
DAYS/WEEK OF PHYSICAL ACTIVITY		APPROXIMATE TIME SPENT

SCHEDULED TEST DATE	
SUBJECT ID #	
PHONE NUMBER	
EMAIL	
POST ADDRESS	

Notes:

APPENDIX C

Physical Activity Readiness and Questionnaire and You Form

Physical Activity Readiness Questionnaire (PAR-Q) and You

Regular physical activity is fun and healthy, and increasingly more people are starting to become more active every day. Being more active is very safe for most people. However, some people should check with their doctor before they start becoming much more physically active.

If you are planning to become much more physically active than you are now, start by answering the seven questions in the box below. If you are between the ages of 15 and 69, the PAR-Q will tell you if you should check with your doctor before you start. If you are over 69 years of age, and you are not used to being very active, check with your doctor Common sense is your best guide when you answer these questions. Please read the questions carefully and answer each one honestly:

YES	NO		
☐	☐	1.	Has your doctor ever said that you have a heart condition and that you should only do physical activity recommended by a doctor?
☐	☐	2.	Do you feel pain in your chest when you do physical activity?
☐	☐	3.	In the past month, have you had chest pain when you were not doing physical activity?
☐	☐	4.	Do you lose your balance because of dizziness or do you ever lose consciousness?
☐	☐	5.	Do you have a bone or joint problem that could be made worse by a change in your physical activity?
☐	☐	6.	Is your doctor currently prescribing drugs (for example, water pills) for your blood pressure or heart condition?
☐	☐	7.	Do you know of any other reason why you should not do physical activity?

If you answered:

Talk to your doctor by phone or in person BEFORE you start becoming much more physically active or BEFORE you have a fitness appraisal. Tell your doctor about the PAR-Q and which questions you answered YES.

- You may be able to do any activity you want – as long as you start slowly and build up gradually. Or, you may need to restrict your activities to those which are safe for you. Talk with your doctor about the kinds of activities you wish to participate in and follow his/her advice.
- Find out which community programs are safe and helpful for you.

If you answered NO honestly to all PAR-Q questions, you can be reasonably sure that you can:
Start becoming much more physically active – begin slowly and build up gradually. This is the safest and easiest way to go.
Take part in a fitness appraisal – this is an excellent way to determine your basic fitness so that you can plan the best way for you to live actively.

Delay becoming much more active:
If you are not feeling well because of a temporary illness such as a cold or a fever – wait until you feel better; or
If you are or may be pregnant – talk to your doctor before you start becoming more active.

Please note: If your health changes so that you then answer YES to any of the above questions, tell your fitness or health professional. Ask whether you should change your physical activity plan.

Informed use of the PAR-Q: The Canadian Society for Exercise Physiology, Health Canada, and their agents assume no liability for persons who undertake physical activity, and if in doubt after completing this questionnaire, consult your doctor prior to physical activity.

I have e read, understood and completed this questionnaire. Any questions I had were answered to my full satisfaction.

Name _____

Signature _____ Date _____

Signature of Parent (if applicable) _____ Witness _____

CONFIDENTIAL

APPENDIX D

Informed Consent Form

TEXAS WOMAN'S UNIVERSITY
SUBJECT CONSENT TO PARTICIPATE IN RESEARCH

TEXAS WOMAN'S UNIVERSITY
CONSENT TO PARTICIPATE IN RESEARCH

Title: Acute and Chronic Effects of Whole Body Heat Therapy on Glucose and Insulin Responses in Healthy Individuals and Type 2 Diabetics.

Investigator: Eric Rivas, MS ..... ericrivas@texashealth.org 361/392-3031
Co-Investigator: Dan Newmire, MS..... dnewmire@twu.edu 319/321-2144
Advisor: Vic Ben-Ezra, PhD..... vbenezra@twu.edu 940/898-2597

You may call the study investigators during regular office hours at PH 116, 940-898-2597 or 361-392-3031.

Instructions:
Please read this consent form carefully and take your time making a decision about whether to participate. As the researchers discuss this consent form with you, please ask him/her to explain any words or information that you do not clearly understand. The purpose of the study, risks, inconveniences, discomforts, and other important information about the study are listed below. If you decide to participate, you will be given a copy of this form to keep.

Explanation and Purpose of the Research

You are being asked to participate in a research study for Mr. Eric Rivas, Doctoral student at Texas Woman's University. This study is being done to investigate the effect of an elevated body temperature and how your body uses sugar in the blood. Normal blood sugar levels need to be maintained. Blood sugar levels that are too high or low can cause health problems such as diabetes, stroke, and cardiovascular disease. This study will investigate the effects of increasing body temperature (during rest) on improving blood sugar levels.

Description of Procedures
As a participant in this study you will be asked to take part in this study because you are either:

- Male between the ages of 18 and 60 years, are overweight, and have type 2 diabetes
- Male or pre and post-menopausal female, Healthy sedentary (exercise less than three days a week), between the ages of 18 and 60 years
- Female and post-menopausal, overweight, and have type 2 diabetes

If you are taking insulin or currently smoke, you are not eligible to be enrolled into this study.

If you volunteer to take part in this research study, you will be asked to sign this consent form and will have the following tests and procedures conducted. All tests and procedures are done solely for the purpose of the study and are not intended to diagnose or treat medical problems.

To complete this project, information will be collected during 22 different days. If you agree to participate in the study, you will be required to visit the laboratory up to 22 times. The first day will involve screening procedures and preliminary testing. You will then complete an experimental whole body passive heat stress (via resting in a warm bath) conditions three days a week over a six week time. Twenty-four hours after the first, eleventh, and twenty second day, you will come into the laboratory to test your body's ability to use glucose (sugar).

Screening Procedures
To help decide if you qualify for this study, the researchers will ask you questions about your health, including medications you take and any surgical procedures you have had.

You may also have the following exams, tests or procedures:

- Physical exam and medical history;
- Hemoglobin A1C: Average blood sugar levels over two to three months;
- Body Mass Index: Measure of human body shape based on body mass divided by the square of your height;
- Waist circumference: Measure of abdominal fat;
- Fasting blood glucose: Blood sugar level measurement after 12 hours (overnight) of abstaining from food consumption;
- 2 h oral glucose tolerance test;
- Vital signs such as blood pressure and heart rate;
- Electrocardiogram (ECG), a tracing of the electrical activity of the heart

If you decide to participate in the study, you are committing to approximately 49.25 hours of testing and having about a 1 cup (1.03 cup) of blood drawn. This study involves twenty-two visits to the laboratory. These visits include one (1) pretesting and familiarization session and eighteen (18) experimental sessions (3 days a week for 6 weeks); and three (3) post-experimental sessions (after 1 day, and 3 and 6 weeks) which will be a 24 hour post experimental session to test (oral glucose tolerance test) your body's ability to use glucose (sugar).

During the course of this study you will have the following tests and procedures:

Preliminary sessions: You will then undergo one preliminary session. The first session will entail obtaining informed written consent, a physical activity questionnaire, measurement of height, weight, and waist circumference and a small blood sample (~2 teaspoons). This blood sample will test hemoglobin A1C levels and a lipid profile, which show the average blood glucose levels over the last two to three months, and fasting glucose levels. You will then be familiarized with all experimental procedures. It will be important to keep nutrition the same before all post experimental sessions. You will be given a food nutrition log and required to record all food intake for 3 days prior to each oral glucose tolerance test session. You will then complete a 2 h oral glucose tolerance test. Following this test, you will then complete a body composition measurement. You will then be fitted with an ambulatory 24hr blood pressure monitor before you leave.

Dual Energy X-ray Absorptiometry (body composition measurement):
Description of Procedure: This procedure measures percent body fat and percent lean tissue mass. All test procedures will be performed by trained personnel with appropriate supervision, and all attempts will be made to minimize the minimal risks associated with your participation in this study. You will then be asked to lie on your back with your legs supported for the duration of the scan (about 5 minutes). During the scan the scanner arm will pass over your body several times.
Potential Risks: This procedure includes exposure to a small amount of radiation. The risk of harm to the body from this radiation exposure is comparable to the everyday risk of driving up to 2 miles in an automobile or smoking up to 2 cigarettes. This procedure has a long history of being used without complications. It is now considered the gold standard for measurement of body composition.
Duration of Procedure: Body composition will take approximately 15 minutes.

Oral temperature (via oral thermistor sensor):
Description of Procedure: In order to monitor your body temperature, the researcher will ask you to insert an oral temperature probe. A fully sterile thermistor (with a new throw away plastic cover) probe will be placed into your mouth directly under the tongue over the duration of the experiment. You will insert the probe at the beginning of each experimental session and remove it before you leave that day.

Potential Risks: You may experience slight irritation. The flexible wire probe will be inserted into your mouth and placed directly under your tongue at the beginning of each session and removed before you leave that day. Clear directions will be given prior to placement of the probe.
Duration of Procedure: Oral temperature will be measured during the entire experiment (approximately 1 hour).

Internal temperature (via rectal probe):
In order to monitor your body temperature, a rectal probe will be used. This is not a requirement of the study; however, if you are willing to take this measure, it will provide us with accurate measurement of your body temperature. You may still participate if you refuse to have this done. The researcher will ask you to insert a rectal temperature probe. You will be asked to insert the probe to a pre-marked depth of approximately 8 to 12 cm. You will insert and remove the probe in a private room. You may not have a rectal probe if you have or have had any heart conditions, inflammatory bowel or colon disease, and/or rectal or anal surgery. You may not use the probe if you currently have hemorrhoids (internal or external), rectal bleeding, diarrhea or fecal impaction in the rectum. You will insert the probe at the beginning of each experimental session and remove it before you leave that day.
Potential Risks: Although it is very rare, it is possible that you could puncture your anus or rectum or get an infection.
Duration of Procedure: Internal temperature will be measured during the entire experiment (approximately 2 hours).

Skin temperature:
Description of Procedure: Skin temperature will be measured by taping temperature probes to your skin at seven sites (chest, shoulder, lower back, abdomen, thigh, calf, and back of neck).
Potential Risks: There is no risk associated with this procedure.
Duration of Procedure: Skin temperature will be measured during the entire experiment (approximately 1 hour).

Heart rate:
Description of Procedure: Heart rate will be measured by wearing a strap placed around your chest that transmits electrical signals.
Potential Risks: There is no risk associated with this procedure.
Duration of Procedure: Heart rate will be measured during the entire experiment (approximately 1 hour).

Blood pressure:
Description of Procedure: Your blood pressure will also be monitored using a cuff placed on your upper arm that is inflated and deflated periodically during the study. A 24 hr blood pressure device will be given to you and will inflate and deflate periodically over 24 hrs.
Potential Risks: Other than some potential discomfort associated with cuff inflation there is no risk to this procedure.
Duration of Procedure: The cuff will be on your upper arm during the measurement of blood pressure. We will take blood pressure measurements at different time points during the experiment. Each measurement will last approximately 30 seconds.

Rating of Thermal Sensation:
Description of Procedure: You will be asked to rate on a standardized scale how hot or cold you feel.
Potential Risks: There is no risk or discomfort associated with this procedure.
Duration of Procedure: You will be asked several times throughout the study to rate your thermal sensation.

Rating of Perceived Exertion:
Description of Procedure: You will be asked to rate on a standardized scale how hard you feel you are exercising.
Potential Risks: There is no risk or discomfort associated with this procedure.
Duration of Procedure: You will be asked several times throughout the study to rate your thermal sensation.

Oxygen Consumption:
Description of Procedure: This measures your body's ability to use oxygen. This involves breathing regular room air through a snorkel-like mouthpiece or facemask during the experiments, and air that you breathe out will be analyzed by a computer.
Potential Risks: There is no risk involved with completing this procedure.
Duration of Procedure: The total duration of the test will be intermittently over the duration of the experiment (5minute intervals over 60 -90minutes).

Finger Prick:
Description of Procedure: Blood samples will be collected from the index finger of the non-dominant hand. Latex gloves will be used. The participant will wash their hands with uncontaminated water and soap. Each sample site will be wiped with a 70% isopropyl alcohol swab before blood extraction. Upon lancing the site, the initial blood drop will be wiped away and then two 50 µL capillary tubes will be filled.

Potential Risks: You may have discomfort, bleeding, and/or bruising. To minimize bruising, pressure will be applied to the site for approximately five minutes after each blood draw.
Duration of Procedure: The amount of time to collect each sample is minimal (45-90 seconds).

Peripheral intravenous catheter during oral glucose tolerance test:
Description of Procedure: A sterile catheter, which is a thin flexible plastic tube, will be inserted into an arm vein so that blood can be taken several times without having multiple sticks with a needle. The nurse will draw blood samples for various chemicals in the body: glucose, insulin and C-peptide, (hormones produced by the pancreas), and lipids (fats).
Potential Risks: There is a small risk of infection and a smaller risk of a blood clot or breakage of the catheter. The likelihood of these complications is remote (about 1 in 10,000) when the procedure is carried out by trained personnel and proper equipment is used, as it will be in your case. There is also a small risk of the catheter perforating (going through) the vein or not being inserted into a blood vessel. Also, you may have discomfort, bleeding, and/or bruising. On a rare occasion, a person may feel dizzy or faint. A trained phlebotomist and proper equipment will be used. Universal precautions will be used during all blood draw procedures. Sites for blood draws will be cleaned with alcohol immediately prior to each venipuncture. Each new needle that is opened will be disposed of in biohazard boxes immediately after use.
Duration of Procedure: The catheter will be in place for the entire experiment of the oral glucose tolerance test (approximately 3 hours per OGTT).

Oral Glucose Tolerance Test
Description of Procedure: During this study, you will undergo an oral glucose tolerance test.
This is a two-hour test that involves several blood samples. On the night before your test, you will eat your last meal and should not eat or drink anything other than water for at least 10 to 12 hours after. For this test, you will have a peripheral intravenous catheter (thin plastic tube described above) inserted into a large vein in your arm. The catheter will allow the study nurse to draw several blood samples from your vein without reinserting a needle each time. The nurse will then give you a sugary substance to drink (75g glucose) over a short period. Blood samples will be drawn every 30 minutes for 120 minutes. The time at which you begin drinking the beverage will count as "0 minute." The nurse will take a total of 6 small samples (10ml each or 0.7 tablespoon) of blood from your vein during the two-hour test (one time before you drink the beverage and four after you drink the beverage). The total amount of blood taken during each test will be 60ml or 4 tablespoons. The results of the oral glucose tolerance test will allow the researchers to observe how your body reacts to sugar.

Potential Risk: You may experience hyperglycemia (high blood sugar) as a result of the oral glucose tolerance test. The participant may find it difficult to drink the extremely sweet glucose (sugary) liquid. Some people feel sick after drinking the glucose liquid and may vomit. It is possible that blood glucose levels may drop very low

toward the end of the test. Symptoms of low blood glucose include weakness, hunger, sweating, and feeling nervous or restless. If levels are very low, the test will be stopped. Hypoglycemia (low blood sugar, <70mg%) may result from prolonged fasting. If the participants show signs of hypoglycemia during the testing session, the test will be terminated. Signs of hypoglycemia include headache, confusion, hallucinations, bizarre behavior, tremors, cold sweat, low body temperature, blurry vision, shaking or trembling, fast heartbeat, sweating, tiredness/ weakness, convulsions, and coma. You will be given a glass of orange juice and monitored until the signs of hypoglycemia subside.
Duration of Procedure: Blood samples will be drawn every 30 minutes for 120 minutes. The oral glucose tolerance test will take approximately 2 hours.

Whole Body Passive Heating:
Description of Procedure: For this procedure, you will rest in a warm water bath set at ~102°F (~39°C). Your internal temperature may increase by approximately 3 °F (i.e. from ~98.7 to ~101.7 °F, but no more than 103°F (39.5°C). Following the procedure, your temperature will be returned to normal by a fan and applying cold ice towels.

Potential Risks: There are slight risks of dehydration, hypotension, and fainting associated with the higher temperature changes. To prevent dehydration and hypotension, fluid will be given to you over the duration of the experiment. Warm water (3% of your nude body weight) will be given over the duration of the experiment to replace fluid loss. You will sit in a seat that will lower you into the warm water and rise when completed. You will not be allowed to stand after the 1 hour experiment until body temperature and blood pressure returns to normal baseline levels. Thermal perception scales will be utilized for this purpose. If that participant feels a 13 on the scale, which is "So hot I am sick and nauseated," the test will stop and the participant will be cooled. Blood pressure will be monitored during the passive heat stress sessions. If the participant's blood pressure exceeds 250/115 mm of Hg or if the participant develops lightheadedness, the experiment will be terminated. Body weight will indicate dehydration. All participants will be given fluid to replace fluid loss. Towels soaked in ice water and a fan will be available during all experimental trials for the purpose of lowering body temperature if the critical temperature of 39.5°C is reached.
Duration of Procedure: The maximum total duration of the heating period will be approximately 60 minutes. The total duration of the cooling period will be approximately 30 minutes.

Body Weight:
Description of Procedure: You will be asked to stand on a scale in a private room and provide a nude body weight. Pre and post body weight measurement will give an indication of fluid loss and hydration status.
Potential Risks: There are no risks associated with this procedure. Warm water will be available for you to drink through the warm bath heating to prevent body fluid loss. You will be given a scale and allowed to weight yourself in a private area to prevent embarrassment.
Duration of Procedure: Each weight measurement will take about 30 seconds.

Waist Circumference:
Description of Procedure: To determine your waist circumference, you will stand with your arms at your sides, feet together, and abdomen relaxed. A horizontal measure will be taken at the narrowest part of your torso above the bellybutton.
Potential Risks: There are no risks associated with this procedure. Your waist will be measured in a private area to prevent embarrassment.
Duration of Procedure: Each waist measurement will take about 30 seconds.

Body Height:
Description of Procedure: You will be asked to stand on a scale which will measure your height.
Potential Risks: There are no risks associated with this procedure.
Duration of Procedure: Each height measurement will take about 30 seconds.

How long can I expect to be in this study?
You will be asked to participate in 22 visits over six week period. You will need to come into the lab for one preliminary visit, eighteen whole body passive heating visits, and then again 24 hours after visit one, eleven, and twenty one of the whole body heat visits. The study will last a total of 6 weeks. Each visit will take approximately 2 to 3.5 hours (See example study design).

Dietary Considerations:
You will be asked to consume a similar diet before each oral glucose tolerance test. For three days before as well as after each session you will keep a dietary record to insure that food intake in terms of total calories and composition (percentages of fat, carbohydrate, and protein) are similar. The glucose tolerance test will occur the next morning after a whole body passive heating session. You will receive counseling on how to keep the dietary record as well as information about keeping a similar diet.

Participation and Benefits
Participation in the study will be of no monetary cost to you. Following completion of the study, you will have the results of the study and your individual results. The subjects will receive information regarding their level of blood pressure, glucose tolerance, body composition, and nutritional intake, lipid profile, and bone density. Participants that complete the study will obtain 100$. If you complete the three day acute only, but not the chronic, you will only receive 50$. This information is supplied free of charge and will increase your awareness of your personal health.

The procedures outlined above have been explained to me by Dr. Vic Ben-Ezra, Eric Rivas, Dan Newmire or other project personnel _____, and I understand that I can contact them at 940-898-2597 or 361-392-3031 if any questions arise. In case of a medical emergency, the fire department's Emergency Medical Team will be alerted. Telephones are available in the testing laboratories.

The researchers will try to prevent any problem that could happen because of this research. You should let the researchers know at once if there is a problem and they will help you. However, TWU does not provide medical services or financial assistance for injuries that might happen because you are taking part in this research. Phone numbers where the investigators may be reached are provided in this form.

Confidentiality will be protected to the extent that is allowed by law. To reduce the possibility of improper disclosure, your name will be kept confidential and will not be associated with the data in any presentation of results. All subjects will be given a code number. Your data will be kept on file in a locked cabinet for a maximum of 5 years after the data are published. All data will be destroyed (shredded) after the five-year period. All data will be discarded in the recycle bin or regular trash, making sure that your name is completely obliterated on any documents or data files. Other personnel, such as a trained phlebotomist will sign a confidentiality agreement.

An offer to answer all of my questions regarding the study have been made and I have been given a copy of the dated and signed consent form. If alternative procedures are more advantageous to me, they have been explained. A description of the possible attendant discomforts and risks reasonably expected have been discussed with me. I understand that I may **withdraw from any portion of the study** at any time. I understand that my participation in this study is completely voluntary and that refusal to participate in any portion of the study will involve no penalty of loss of benefits to which I am otherwise entitled.

Approved by the
Texas Woman's University
Institutional Review Board

Approved: August 2, 2014

_____
Initials

Questions Regarding the Study

You will be given a copy of this signed and dated consent form to keep. If you have any questions about the research study you should ask the researchers; their phone numbers are at the top of this form. If you have questions about your rights as a participant in this research or the way this study has been conducted, you may contact the Texas Woman's University Office of Research and Sponsored Programs at 940-898-3378 or via e-mail at IRB@twu.edu.

_____ _____

Signature of Participant Date

*If you would like to know the results of this study tell us where you want them to be sent:

Email: _____

or

Address:

_____

_____

_____

Approved by the
Texas Woman's University
Institutional Review Board

Approved: August 2, 2014

APPENDIX E

Medical History Form

Medical History Form

Name: _____Date:_____
Age: _____ Sex: _ M _ F
Physician's Name_____
Physician's Phone Number (_____)_____
Person to contact in case of Emergency:
Name_____ Date_____ Phone _____
Are you taking any medication or drugs? If so, please list medication, dose, and reason.
_____
_____
Does your physician know you are participating in this exercise program?
_____
_____
Describe any physical activity you do somewhat regularly.
_____
_____

Do you now, or have you had in the past: ***Yes No***

1. History of heart problems, chest pain or stroke ☐ ☐
2. Increased blood pressure ☐ ☐
3. Any chronic illness or condition ☐ ☐
4. Difficulty with physical exercise ☐ ☐
5. Advice from physician not to exercise ☐ ☐
6. Recent surgery (last 12 months) ☐ ☐
7. Pregnancy (now or within last 3 months) ☐ ☐
8. History of breathing or lung problems ☐ ☐
9. Muscle, joint or back disorder, or ☐ ☐
   any previous injury still affecting you
10. Diabetes or thyroid condition ☐ ☐
11. Cigarette smoking habit ☐ ☐
12. Obesity (more than 20% over ideal body weight) ☐ ☐
13. Increased blood cholesterol ☐ ☐
14. History of heart problems in immediate family ☐ ☐
15. Hernia, or any condition that may be aggravated ☐ ☐
    by lifting weights

Please explain any "yes" answers below:

_____
_____
_____
_____
_____
_____

APPENDIX F

Thermal Data Forms

Acute and Chronic whole body heat therapy study

Data collection

FILE ID: _____

Name: _____ Warm bath day: _____

Date: _____ Time of day at arrival: _____

Pre In-Tank Nude Body Weight:_____(kg) **ht:** _____(in)

Pre-immersion (baseline data)

Minute	**0**	**10**	**20**	**30**
Oral Temperature				
Skin Temperature				
Heart Rate				
VO2 (parvo)				
Blood Pressure Systolic				
Diastolic				

3% of nude body wt	
Fluid Vol.	_____ mL
per Feeding	mL

(Start temperature readings 5minutes before data collection time)

Minute	**0**	**10**	**20**	**30**	**40**	**50**	**60**
Oral Temp							
Water Temp							
Skin Temp							
Thermal Sensation							
Heart Rate							
VO2 (parvo)							
Blood Pressure Systolic							
Diastolic							

Post heat data collection (Immediately out of tank)

Minute	**0**	**5**	**10**	**20**	**30**	**40**	**50**	**60**
Oral Temperature								
Skin Temperature								
Heart Rate								
VO2 (parvo)								
Blood Pressure Systolic								
Diastolic								

Resting Metabolic Rate: VO2 for 5minutes.

Blood Pressure: Sitting upright, relaxed, and forearm at heart level. Take BP three times at 1min intervals (Average of 3 measurements).

APPENDIX G

Thermal Perception Scale

Perception of Thermal Sensation Scale	
1	So cold I am helpless
2	Numb with cold
3	Very cold
4	Cold
5	Uncomfortable cold
6	Cool but fairly comfortable
7	Comfortable
8	Warm but fairly comfortable
9	Uncomfortably warm
10	Hot
11	Very hot
12	Almost as hot as I can stand
13	So hot I am sick and nauseated

Lee, et. al. 2010

APPENDIX H

RMANOVA Main Effects and Pairwise Comparison Tables

Table 15

RM ANOVA Main Effects for Core Body Temperature during Hyperthermia and Control Treatments

Source		Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared	Noncent. Parameter	Observed Power[a]
Time	Sphericity Assumed	13.41	7.00	1.92	106.79	.000	0.870	747.50	1.000
	Greenhouse-Geisser	13.41	2.54	5.28	106.79	.000	0.870	271.48	1.000
Time * Group	Sphericity Assumed	0.26	7.00	0.04	2.08	.051	0.115	14.58	0.778
	Greenhouse-Geisser	0.26	2.54	0.10	2.08	.126	0.115	5.30	0.455
Error(Time)	Sphericity Assumed	2.01	112.00	0.02					
	Greenhouse-Geisser	2.01	40.68	0.05					
CONDT	Sphericity Assumed	41.63	1.00	41.63	156.33	.000	0.907	156.33	1.000
	Greenhouse-Geisser	41.63	1.00	41.63	156.33	.000	0.907	156.33	1.000
CONDT * Group	Sphericity Assumed	0.15	1.00	0.15	0.55	.469	0.033	0.55	0.107
	Greenhouse-Geisser	0.15	1.00	0.15	0.55	.469	0.033	0.55	0.107
Error(CONDT)	Sphericity Assumed	4.26	16.00	0.27					
	Greenhouse-Geisser	4.26	16.00	0.27					
Time * CONDT	Sphericity Assumed	23.17	7.00	3.31	178.44	.000	0.918	1249.11	1.000
	Greenhouse-Geisser	23.17	2.49	9.30	178.44	.000	0.918	444.47	1.000
Time * CONDT * Group	Sphericity Assumed	0.06	7.00	0.01	0.49	.840	.030	3.43	.206
	Greenhouse-Geisser	0.06	2.49	0.03	0.49	.657	.030	1.22	.133
Error(Time*CONDT)	Sphericity Assumed	2.08	112.00	0.02					
	Greenhouse-Geisser	2.08	39.85	0.05					

a. Computed using alpha = .05, Mauchly's test indicated that the assumption of sphericity had been violated, $X^2(27) = 88.9$, P = .000, therefor degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity (.363).

Table 16

Pairwise Comparisons for Core Body Temperature during Hyperthermia and Control Treatments

(I) Time	(J) Time	Mean Difference (I-J)	Std. Error	Sig.[a]	95% Confidence Lower Bound	95% Confidence Upper Bound
1	2	.000	.030	1.000	-.113	.113
	3	-.019	.031	1.000	-.135	.096
	4	-.083	.040	1.000	-.233	.066
	5	-.244*	.043	.001	-.404	-.085
	6	-.381*	.046	.000	-.554	-.207
	7	-.489*	.046	.000	-.662	-.316
	8	-.564*	.049	.000	-.745	-.382

Table 17

RM ANOVA Main Effects for Core Body Temperature during Recovery from Hyperthermia and Control Treatments

Source		Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared	Noncent. Parameter	Observed Power[a]
Time	Sphericity Assumed	14.21	7.00	2.03	87.31	.000	0.845	611.14	1.000
	Greenhouse-Geisser	14.21	3.03	4.69	87.31	.000	0.845	264.36	1.000
Time * Group	Sphericity Assumed	0.14	7.00	0.02	0.84	.558	0.050	5.87	0.347
	Greenhouse-Geisser	0.14	3.03	0.05	0.84	.481	0.050	2.54	0.219
Error(Time)	Sphericity Assumed	2.60	112.00	0.02					
	Greenhouse-Geisser	2.60	48.45	0.05					
CONDT	Sphericity Assumed	78.65	1.00	78.65	300.16	.000	0.949	300.16	1.000
	Greenhouse-Geisser	78.65	1.00	78.65	300.16	.000	0.949	300.16	1.000
CONDT * Group	Sphericity Assumed	1.04	1.00	1.04	3.97	.064	0.199	3.97	0.465
	Greenhouse-Geisser	1.04	1.00	1.04	3.97	.064	0.199	3.97	0.465
Error(CONDT)	Sphericity Assumed	4.19	16.00	0.26					
	Greenhouse-Geisser	4.19	16.00	0.26					
Time * CONDT	Sphericity Assumed	19.97	7.00	2.85	156.87	.000	0.907	1098.11	1.000
	Greenhouse-Geisser	19.97	2.82	7.08	156.87	.000	0.907	442.63	1.000
Time * CONDT * Group	Sphericity Assumed	0.53	7.00	0.08	4.18	.000	.207	29.24	.985
	Greenhouse-Geisser	0.53	2.82	0.19	4.18	.012	.207	11.78	.806
Error(Time*CONDT)	Sphericity Assumed	2.04	112.00	0.02					
	Greenhouse-Geisser	2.04	45.15	0.05					

a. Computed using alpha = .05, Mauchly's test indicated that the assumption of sphericity had been violated, $X^2(27) = 76.6$, p = .000, therefor degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity (.578).

Table 18

Pairwise Comparisons for ore Body Temperature during Recovery from Hyperthermia and Control Treatments

(I) Time	(J) Time	Mean Difference (I-J)	Std. Error	Sig.[a]	95% Confidence Lower Bound	95% Confidence Upper Bound
1	2	-.603*	.050	.000	-.790	-.416
	3	-.594*	.049	.000	-.776	-.412
	4	-.453*	.046	.000	-.623	-.282
	5	-.292*	.040	.000	-.440	-.143
	6	-.178*	.033	.002	-.303	-.053
	7	-0.141667	.045	.166	-.309	.025
	8	-0.047222	.045	1.000	-.215	.121

Table 19

RM ANOVA Main Effects for Mean Skin Temperature during Hyperthermia and Control Treatments

Source		Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared	Noncent. Parameter	Observed Power[a]
Time	Sphericity Assumed	318.79	7.00	45.54	314.85	.000	0.952	2203.98	1.000
	Greenhouse-Geisser	318.79	2.56	124.30	314.85	.000	0.952	807.51	1.000
Time * Group	Sphericity Assumed	0.88	7.00	0.13	0.87	.533	0.052	6.08	0.360
	Greenhouse-Geisser	0.88	2.56	0.34	0.87	.450	0.052	2.23	0.209
Error(Time)	Sphericity Assumed	16.20	112.00	0.14					
	Greenhouse-Geisser	16.20	41.04	0.39					
CONDT	Sphericity Assumed	2276.44	1.00	2276.44	633.91	.000	0.975	633.91	1.000
	Greenhouse-Geisser	2276.44	1.00	2276.44	633.91	.000	0.975	633.91	1.000
CONDT * Group	Sphericity Assumed	3.67	1.00	3.67	1.02	.327	0.060	1.02	0.158
	Greenhouse-Geisser	3.67	1.00	3.67	1.02	.327	0.060	1.02	0.158
Error(CONDT)	Sphericity Assumed	57.46	16.00	3.59					
	Greenhouse-Geisser	57.46	16.00	3.59					
Time * CONDT	Sphericity Assumed	302.42	7.00	43.20	312.08	.000	0.951	2184.58	1.000
	Greenhouse-Geisser	302.42	2.48	122.11	312.08	.000	0.951	772.89	1.000
Time * CONDT * Group	Sphericity Assumed	1.10	7.00	0.16	1.14	.346	.066	7.95	.470
	Greenhouse-Geisser	1.10	2.48	0.44	1.14	.340	.066	2.81	.259
Error(Time*CONDT)	Sphericity Assumed	15.50	112.00	0.14					
	Greenhouse-Geisser	15.50	39.62	0.39					

a. Computed using alpha = .05, Mauchly's test indicated that the assumption of sphericity had been violated, $X^2(27) = 83.5$, p = .000, therefor degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity (.366).

Table 20

Pairwise Comparisons for Mean Skin Temperature during Hyperthermia and Control Treatments

(I) Time	(J) Time	Mean Difference (I-J)	Std. Error	Sig.[a]	95% Confidence Lower Bound	95% Confidence Upper Bound
1	2	-3.019*	.145	.000	-3.561	-2.478
	3	-3.119*	.154	.000	-3.695	-2.544
	4	-3.144*	.136	.000	-3.652	-2.637
	5	-3.244*	.126	.000	-3.715	-2.774
	6	-3.239*	.146	.000	-3.785	-2.693
	7	-3.253*	.138	.000	-3.767	-2.738
	8	-3.194*	.128	.000	-3.672	-2.716

Table 21

RM ANOVA Main Effects for Mean Skin Temperature during Recovery from Hyperthermia and Control Treatments

Source		Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared	Noncent. Parameter	Observed Power[a]
Time	Sphericity Assumed	84.75	7.00	12.11	51.80	.000	0.764	362.57	1.000
	Greenhouse-Geisser	84.75	3.52	24.11	51.80	.000	0.764	182.09	1.000
Time * Group	Sphericity Assumed	3.19	7.00	0.46	1.95	.068	0.109	13.64	0.744
	Greenhouse-Geisser	3.19	3.52	0.91	1.95	.123	0.109	6.85	0.517
Error(Time)	Sphericity Assumed	26.18	112.00	0.23					
	Greenhouse-Geisser	26.18	56.25	0.47					
CONDT	Sphericity Assumed	0.05	1.00	0.05	0.01	.934	0.000	0.01	0.051
	Greenhouse-Geisser	0.05	1.00	0.05	0.01	.934	0.000	0.01	0.051
CONDT * Group	Sphericity Assumed	0.92	1.00	0.92	0.12	.731	0.008	0.12	0.062
	Greenhouse-Geisser	0.92	1.00	0.92	0.12	.731	0.008	0.12	0.062
Error(CONDT)	Sphericity Assumed	120.93	16.00	7.56					
	Greenhouse-Geisser	120.93	16.00	7.56					
Time * CONDT	Sphericity Assumed	69.40	7.00	9.91	43.50	.000	0.731	304.48	1.000
	Greenhouse-Geisser	69.40	2.68	25.89	43.50	.000	0.731	116.60	1.000
Time * CONDT * Group	Sphericity Assumed	2.42	7.00	0.35	1.52	.169	.087	10.61	.613
	Greenhouse-Geisser	2.42	2.68	0.90	1.52	.227	.087	4.06	.351
Error(Time*CONDT)	Sphericity Assumed	25.53	112.00	0.23					
	Greenhouse-Geisser	25.53	42.89	0.60					

a. Computed using alpha = .05, Mauchly's test indicated that the assumption of sphericity had been violated, $X^2(27) = 72.9$, p = .000, therefor degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity (.502).

Table 22

Pairwise Comparisons for Mean Skin Temperature during Recovery from Hyperthermia and Control Treatments

(I) Time	(J) Time	Mean Difference (I-J)	Std. Error	Sig.[a]	95% Confidence Lower Bound	95% Confidence Upper Bound
1	2	-.894*	0.159	0.001	-1.489	-0.299
	3	-0.550	0.150	0.057	-1.110	0.010
	4	-0.061	0.139	1.000	-0.580	0.458
	5	0.281	0.119	0.897	-0.166	0.727
	6	.486*	0.118	0.023	0.043	0.929
	7	.656*	0.131	0.004	0.166	1.145
	8	.747*	0.152	0.004	0.178	1.317

Table 23

RM ANOVA Main Effects for Mean Body Temperature during Hyperthermia and Control Treatments

Source		Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared	Noncent. Parameter	Observed Power[a]
Time	Sphericity Assumed	57.20	7.00	8.17	351.00	.000	0.956	2457.01	1.000
	Greenhouse-Geisser	57.20	2.40	23.81	351.00	.000	0.956	843.19	1.000
Time * Group	Sphericity Assumed	0.08	7.00	0.01	0.47	.852	0.029	3.32	0.199
	Greenhouse-Geisser	0.08	2.40	0.03	0.47	.661	0.029	1.14	0.128
Error(Time)	Sphericity Assumed	2.61	112.00	0.02					
	Greenhouse-Geisser	2.61	38.44	0.07					
CONDT	Sphericity Assumed	427.54	1.00	427.54	684.90	.000	0.977	684.90	1.000
	Greenhouse-Geisser	427.54	1.00	427.54	684.90	.000	0.977	684.90	1.000
CONDT * Group	Sphericity Assumed	0.02	1.00	0.02	0.02	.878	0.002	0.02	0.052
	Greenhouse-Geisser	0.02	1.00	0.02	0.02	.878	0.002	0.02	0.052
Error(CONDT)	Sphericity Assumed	9.99	16.00	0.62					
	Greenhouse-Geisser	9.99	16.00	0.62					
Time * CONDT	Sphericity Assumed	66.76	7.00	9.54	411.20	.000	0.963	2878.37	1.000
	Greenhouse-Geisser	66.76	2.68	24.90	411.20	.000	0.963	1102.56	1.000
Time * CONDT * Group	Sphericity Assumed	0.13	7.00	0.02	0.83	.566	.049	5.79	.343
	Greenhouse-Geisser	0.13	2.68	0.05	0.83	.474	.049	2.22	.205
Error(Time*CONDT)	Sphericity Assumed	2.60	112.00	0.02					
	Greenhouse-Geisser	2.60	42.90	0.06					

a. Computed using alpha = .05, Mauchly's test indicated that the assumption of sphericity had been violated, $X^2(27) = 82.3$, p = .000, therefor degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity (.343).

Table 24

Pairwise Comparisons for Mean Body Temperature during Hyperthermia and Control Treatments

(I) Time	(J) Time	Mean Difference (I-J)	Std. Error	Sig.[a]	95% Confidence Lower Bound	95% Confidence Upper Bound
1	2	-1.036*	0.052	0.000	-1.231	-0.841
	3	-1.094*	0.056	0.000	-1.302	-0.887
	4	-1.147*	0.058	0.000	-1.366	-0.929
	5	-1.278*	0.050	0.000	-1.464	-1.091
	6	-1.372*	0.057	0.000	-1.586	-1.158
	7	-1.450*	0.062	0.000	-1.683	-1.217
	8	-1.481*	0.062	0.000	-1.713	-1.248

Table 25

RM ANOVA Main Effects for Mean Body Temperature during Recovery from Hyperthermia and Control Treatments

Source		Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared	Noncent. Parameter	Observed Power[a]
Time	Sphericity Assumed	29.65	7.00	4.24	115.24	.000	0.878	806.70	1.000
	Greenhouse-Geisser	29.65	3.42	8.66	115.24	.000	0.878	394.56	1.000
Time * Group	Sphericity Assumed	0.73	7.00	0.10	2.84	.009	0.151	19.86	0.907
	Greenhouse-Geisser	0.73	3.42	0.21	2.84	.040	0.151	9.71	0.689
Error(Time)	Sphericity Assumed	4.12	112.00	0.04					
	Greenhouse-Geisser	4.12	54.78	0.08					
CONDT	Sphericity Assumed	33.76	1.00	33.76	33.55	.000	0.677	33.55	1.000
	Greenhouse-Geisser	33.76	1.00	33.76	33.55	.000	0.677	33.55	1.000
CONDT * Group	Sphericity Assumed	0.02	1.00	0.02	0.02	.881	0.001	0.02	0.052
	Greenhouse-Geisser	0.02	1.00	0.02	0.02	.881	0.001	0.02	0.052
Error(CONDT)	Sphericity Assumed	16.10	16.00	1.01					
	Greenhouse-Geisser	16.10	16.00	1.01					
Time * CONDT	Sphericity Assumed	28.05	7.00	4.01	116.95	.000	0.880	818.68	1.000
	Greenhouse-Geisser	28.05	2.93	9.56	116.95	.000	0.880	343.24	1.000
Time * CONDT * Group	Sphericity Assumed	0.39	7.00	0.06	1.61	.139	.092	11.28	.645
	Greenhouse-Geisser	0.39	2.93	0.13	1.61	.200	.092	4.73	.392
Error(Time*CONDT)	Sphericity Assumed	3.84	112.00	0.03					
	Greenhouse-Geisser	3.84	46.96	0.08					

a. Computed using alpha = .05, Mauchly's test indicated that the assumption of sphericity had been violated, $X^2(27) = 79.0$, p = .000, therefor degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity (.489).

Table 26

Pairwise Comparisons for Mean Body Temperature during Recovery from Hyperthermia and Control Treatments

(I) Time	(J) Time	Mean Difference (I-J)	Std. Error	Sig.[a]	95% Confidence Lower Bound	95% Confidence Upper Bound
1	2	-.697*	0.060	0.000	-0.921	-0.474
	3	-.578*	0.051	0.000	-0.767	-0.389
	4	-.311*	0.057	0.001	-0.524	-0.098
	5	-0.089	0.045	1.000	-0.257	0.079
	6	0.075	0.055	1.000	-0.131	0.281
	7	0.142	0.055	0.567	-0.064	0.347
	8	.242*	0.059	0.022	0.023	0.461

Table 27

RM ANOVA Main Effects for Phsyiological Strain Index during Hyperthermia and Control Treatments

Source		Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared	Noncent. Parameter	Observed Power[a]
Time	Sphericity Assumed	732.49	7.00	104.64	108.40	.000	0.871	758.83	1.000
	Greenhouse-Geisser	732.49	3.46	211.43	108.40	.000	0.871	375.56	1.000
Time * Group	Sphericity Assumed	3.15	7.00	0.45	0.47	.857	0.028	3.27	0.197
	Greenhouse-Geisser	3.15	3.46	0.91	0.47	.734	0.028	1.62	0.145
Error(Time)	Sphericity Assumed	108.11	112.00	0.97					
	Greenhouse-Geisser	108.11	55.43	1.95					
CONDT	Sphericity Assumed	2244.50	1.00	2244.50	175.58	.000	0.916	175.58	1.000
	Greenhouse-Geisser	2244.50	1.00	2244.50	175.58	.000	0.916	175.58	1.000
CONDT * Group	Sphericity Assumed	46.72	1.00	46.72	3.66	.074	0.186	3.66	0.435
	Greenhouse-Geisser	46.72	1.00	46.72	3.66	.074	0.186	3.66	0.435
Error(CONDT)	Sphericity Assumed	204.53	16.00	12.78					
	Greenhouse-Geisser	204.53	16.00	12.78					
Time * CONDT	Sphericity Assumed	1032.67	7.00	147.52	162.65	.000	0.910	1138.56	1.000
	Greenhouse-Geisser	1032.67	3.44	300.58	162.65	.000	0.910	558.81	1.000
Time * CONDT * Group	Sphericity Assumed	10.00	7.00	1.43	1.58	.150	.090	11.03	.633
	Greenhouse-Geisser	10.00	3.44	2.91	1.58	.201	.090	5.41	.420
Error(Time*CONDT)	Sphericity Assumed	101.58	112.00	0.91					
	Greenhouse-Geisser	101.58	54.97	1.85					

a. Computed using alpha = .05, Mauchly's test indicated that the assumption of sphericity had been violated, $X^2(27) = 45.77$, p = .017, therefor degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity (.495).

Table 28

Pairwise Comparisons for Phsyiological Strain Index during Hyperthermia and Control Treatments

(I) Time	(J) Time	Mean Difference (I-J)	Std. Error	Sig.[a]	95% Confidence Lower Bound	95% Confidence Upper Bound
1	2	-0.361	0.190	1.000	-1.071	0.349
	3	-0.694	0.222	0.183	-1.526	0.137
	4	-1.722*	0.306	0.001	-2.865	-0.579
	5	-2.833*	0.336	0.000	-4.089	-1.578
	6	-3.333*	0.275	0.000	-4.362	-2.305
	7	-3.833*	0.257	0.000	-4.794	-2.873
	8	-4.500*	0.269	0.000	-5.505	-3.495

Table 29

RM ANOVA Main Effects for Phsyiological Strain Index during Recovery from Hyperthermia and Control Treatments

Source		Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared	Noncent. Parameter	Observed Power[a]
Time	Sphericity Assumed	532.89	7.00	76.13	39.35	.000	0.711	275.46	1.000
	Greenhouse-Geisser	532.89	2.76	192.88	39.35	.000	0.711	108.72	1.000
Time * Group	Sphericity Assumed	9.89	7.00	1.41	0.73	.647	0.044	5.11	0.302
	Greenhouse-Geisser	9.89	2.76	3.58	0.73	.529	0.044	2.02	0.187
Error(Time)	Sphericity Assumed	216.67	112.00	1.93					
	Greenhouse-Geisser	216.67	44.20	4.90					
CONDT	Sphericity Assumed	2250.09	1.00	2250.09	201.91	.000	0.927	201.91	1.000
	Greenhouse-Geisser	2250.09	1.00	2250.09	201.91	.000	0.927	201.91	1.000
CONDT * Group	Sphericity Assumed	103.92	1.00	103.92	9.33	.008	0.368	9.33	0.818
	Greenhouse-Geisser	103.92	1.00	103.92	9.33	.008	0.368	9.33	0.818
Error(CONDT)	Sphericity Assumed	178.31	16.00	11.14					
	Greenhouse-Geisser	178.31	16.00	11.14					
Time * CONDT	Sphericity Assumed	698.33	7.00	99.76	63.96	.000	0.800	447.71	1.000
	Greenhouse-Geisser	698.33	2.66	262.15	63.96	.000	0.800	170.38	1.000
Time * CONDT * Group	Sphericity Assumed	17.16	7.00	2.45	1.57	.151	.089	11.00	.632
	Greenhouse-Geisser	17.16	2.66	6.44	1.57	.214	.089	4.19	.362
Error(Time*CONDT)	Sphericity Assumed	174.69	112.00	1.56					
	Greenhouse-Geisser	174.69	42.62	4.10					

a. Computed using alpha = .05, Mauchly's test indicated that the assumption of sphericity had been violated, $X^2(27) = 67.27$, p = .000, therefor degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity (.395).

Table 30

Pairwise Comparisons for Phsyiological Strain Index during Recovery from Hyperthermia and Control Treatments

(I) Time	(J) Time	Mean Difference (I-J)	Std. Error	Sig.[a]	95% Confidence Lower Bound	95% Confidence Upper Bound
1	2	-4.250*	0.356	0.000	-5.580	-2.920
	3	-3.389*	0.324	0.000	-4.601	-2.176
	4	-2.500*	0.328	0.000	-3.727	-1.273
	5	-1.750*	0.358	0.005	-3.089	-0.411
	6	-0.889	0.371	0.812	-2.275	0.497
	7	-0.917	0.372	0.716	-2.309	0.476
	8	-0.833	0.407	1.000	-2.357	0.690

Table 31

RM ANOVA Main Effects for Perception of Thermal Sensation during Hyperthermia and Control Treatments and Recovery

Source		Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared	Noncent. Parameter	Observed Power[a]
Time	Sphericity Assumed	83.16	7.00	11.88	33.69	.000	0.678	235.80	1.000
	Greenhouse-Geisser	83.16	2.81	29.58	33.69	.000	0.678	94.72	1.000
Time * Group	Sphericity Assumed	0.77	7.00	0.11	0.31	.947	0.019	2.20	0.141
	Greenhouse-Geisser	0.77	2.81	0.28	0.31	.803	0.019	0.88	0.104
Error(Time)	Sphericity Assumed	39.50	112.00	0.35					
	Greenhouse-Geisser	39.50	44.99	0.88					
CONDT	Sphericity Assumed	286.00	1.00	286.00	140.68	.000	0.898	140.68	1.000
	Greenhouse-Geisser	286.00	1.00	286.00	140.68	.000	0.898	140.68	1.000
CONDT * Group	Sphericity Assumed	1.53	1.00	1.53	0.75	.398	0.045	0.75	0.129
	Greenhouse-Geisser	1.53	1.00	1.53	0.75	.398	0.045	0.75	0.129
Error(CONDT)	Sphericity Assumed	32.53	16.00	2.03					
	Greenhouse-Geisser	32.53	16.00	2.03					
Time * CONDT	Sphericity Assumed	88.08	7.00	12.58	33.09	.000	0.674	231.66	1.000
	Greenhouse-Geisser	88.08	2.87	30.65	33.09	.000	0.674	95.10	1.000
Time * CONDT * Group	Sphericity Assumed	0.77	7.00	0.11	0.29	.956	.018	2.04	.133
	Greenhouse-Geisser	0.77	2.87	0.27	0.29	.823	.018	0.84	.101
Error(Time*CONDT)	Sphericity Assumed	42.58	112.00	0.38					
	Greenhouse-Geisser	42.58	45.98	0.93					

a. Computed using alpha = .05, Mauchly's test indicated that the assumption of sphericity had been violated, $X^2(27) = 61.93$, P = .000, therefor degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity (.402).

Table 32

Pairwise Comparisons for Perception of Thermal Sensation during Hyperthermia and Control Treatments and Recovery

(I) Time	(J) Time	Mean Difference (I-J)	Std. Error	Sig.[a]	95% Confidence Lower Bound	95% Confidence Upper Bound
1	2	-.500*	0.117	0.016	-0.938	-0.062
	3	-.611*	0.098	0.000	-0.978	-0.244
	4	-.694*	0.103	0.000	-1.080	-0.309
	5	-.972*	0.121	0.000	-1.425	-0.519
	6	-1.111*	0.142	0.000	-1.641	-0.581
	7	-1.528*	0.192	0.000	-2.246	-0.810
	8	-1.778*	0.194	0.000	-2.505	-1.051

Table 33

RM ANOVA Main Effects for Heart Rate during Hyperthermia and Control Treatments

Source		Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared	Noncent. Parameter	Observed Power[a]
Time	Sphericity Assumed	8749.60	7.00	1249.94	60.20	.000	0.790	421.37	1.000
	Greenhouse-Geisser	8749.60	3.47	2524.13	60.20	.000	0.790	208.66	1.000
Time * Group	Sphericity Assumed	137.28	7.00	19.61	0.94	.476	0.056	6.61	0.392
	Greenhouse-Geisser	137.28	3.47	39.60	0.94	.436	0.056	3.27	0.262
Error(Time)	Sphericity Assumed	2325.63	112.00	20.76					
	Greenhouse-Geisser	2325.63	55.46	41.93					
CONDT	Sphericity Assumed	59225.35	1.00	59225.35	257.68	.000	0.942	257.68	1.000
	Greenhouse-Geisser	59225.35	1.00	59225.35	257.68	.000	0.942	257.68	1.000
CONDT * Group	Sphericity Assumed	72.00	1.00	72.00	0.31	.583	0.019	0.31	0.082
	Greenhouse-Geisser	72.00	1.00	72.00	0.31	.583	0.019	0.31	0.082
Error(CONDT)	Sphericity Assumed	3677.40	16.00	229.84					
	Greenhouse-Geisser	3677.40	16.00	229.84					
Time * CONDT	Sphericity Assumed	11341.49	7.00	1620.21	81.91	.000	0.837	573.35	1.000
	Greenhouse-Geisser	11341.49	4.10	2763.91	81.91	.000	0.837	336.10	1.000
Time * CONDT * Group	Sphericity Assumed	137.28	7.00	19.61	0.99	.441	.058	6.94	.411
	Greenhouse-Geisser	137.28	4.10	33.45	0.99	.420	.058	4.07	.300
Error(Time*CONDT)	Sphericity Assumed	2215.49	112.00	19.78					
	Greenhouse-Geisser	2215.49	65.65	33.74					

a. Computed using alpha = .05, Mauchly's test indicated that the assumption of sphericity had been violated, X2(27) = 67.6, P = .000, therefor degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity (.495).

Table 34

Pairwise Comparisons for Heart Rate during Hyperthermia and Control Treatments

(I) Time	(J) Time	Mean Difference (I-J)	Std. Error	Sig.[a]	95% Confidence Lower Bound	95% Confidence Upper Bound
1	2	-5.722*	0.757	0.000	-8.555	-2.890
	3	-5.778*	1.271	0.009	-10.533	-1.023
	4	-11.417*	1.364	0.000	-16.519	-6.315
	5	-15.139*	1.604	0.000	-21.138	-9.140
	6	-12.889*	0.866	0.000	-16.126	-9.652
	7	-14.333*	1.038	0.000	-18.216	-10.450
	8	-17.222*	1.102	0.000	-21.343	-13.101

Table 35

RM ANOVA Main Effects for Heart Rate during Recovery from Hyperthermia and Control Treatments

Source		Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared	Noncent. Parameter	Observed Power[a]
Time	Sphericity Assumed	3628.14	7.00	518.31	13.64	.000	0.460	95.48	1.000
	Greenhouse-Geisser	3628.14	3.45	1053.10	13.64	.000	0.460	46.99	1.000
Time * Group	Sphericity Assumed	117.22	7.00	16.75	0.44	.875	0.027	3.08	0.187
	Greenhouse-Geisser	117.22	3.45	34.02	0.44	.751	0.027	1.52	0.139
Error(Time)	Sphericity Assumed	4255.83	112.00	38.00					
	Greenhouse-Geisser	4255.83	55.12	77.21					
CONDT	Sphericity Assumed	25256.28	1.00	25256.28	84.35	.000	0.841	84.35	1.000
	Greenhouse-Geisser	25256.28	1.00	25256.28	84.35	.000	0.841	84.35	1.000
CONDT * Group	Sphericity Assumed	1196.42	1.00	1196.42	4.00	.063	0.200	4.00	0.468
	Greenhouse-Geisser	1196.42	1.00	1196.42	4.00	.063	0.200	4.00	0.468
Error(CONDT)	Sphericity Assumed	4790.61	16.00	299.41					
	Greenhouse-Geisser	4790.61	16.00	299.41					
Time * CONDT	Sphericity Assumed	4711.47	7.00	673.07	21.21	.000	0.570	148.50	1.000
	Greenhouse-Geisser	4711.47	2.89	1627.92	21.21	.000	0.570	61.40	1.000
Time * CONDT * Group	Sphericity Assumed	117.22	7.00	16.75	0.53	.812	.032	3.69	.220
	Greenhouse-Geisser	117.22	2.89	40.50	0.53	.659	.032	1.53	.148
Error(Time*CONDT)	Sphericity Assumed	3553.50	112.00	31.73					
	Greenhouse-Geisser	3553.50	46.31	76.74					

a. Computed using alpha = .05, Mauchly's test indicated that the assumption of sphericity had been violated, X2(27) = 51.7, P = .004, therefor degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity (.492).

Table 36

Pairwise Comparisons for Heart Rate during Recovery from Hyperthermia and Control Treatments

(I) Time	(J) Time	Mean Difference (I-J)	Std. Error	Sig.[a]	95% Confidence Lower Bound	95% Confidence Upper Bound
1	2	-11.972*	1.504	0.000	-17.598	-6.346
	3	-7.167*	1.450	0.004	-12.588	-1.746
	4	-5.917*	1.234	0.006	-10.531	-1.302
	5	-5.889*	1.570	0.049	-11.760	-0.018
	6	-1.917	1.753	1.000	-8.471	4.638
	7	-1.667	1.615	1.000	-7.708	4.375
	8	-4.389	1.287	0.100	-9.200	0.423

RM ANOVA Main Effects for the Sensation of Thermal Perception during hyperthermia and control treatments

Table 37

RM ANOVA Main Effects for Phsyiolgical Stain Index during Hyperthermia and Control Treatments

Source		Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared	Noncent. Parameter	Observed Power[a]
Time	Sphericity Assumed	732.49	7.00	104.64	108.40	.000	0.871	758.83	1.000
	Greenhouse-Geisser	732.49	3.46	211.43	108.40	.000	0.871	375.56	1.000
Time * Group	Sphericity Assumed	3.15	7.00	0.45	0.47	.857	0.028	3.27	0.197
	Greenhouse-Geisser	3.15	3.46	0.91	0.47	.734	0.028	1.62	0.145
Error(Time)	Sphericity Assumed	108.11	112.00	0.97					
	Greenhouse-Geisser	108.11	55.43	1.95					
CONDT	Sphericity Assumed	2244.50	1.00	2244.50	175.58	.000	0.916	175.58	1.000
	Greenhouse-Geisser	2244.50	1.00	2244.50	175.58	.000	0.916	175.58	1.000
CONDT * Group	Sphericity Assumed	46.72	1.00	46.72	3.66	.074	0.186	3.66	0.435
	Greenhouse-Geisser	46.72	1.00	46.72	3.66	.074	0.186	3.66	0.435
Error(CONDT)	Sphericity Assumed	204.53	16.00	12.78					
	Greenhouse-Geisser	204.53	16.00	12.78					
Time * CONDT	Sphericity Assumed	1032.67	7.00	147.52	162.65	.000	0.910	1138.56	1.000
	Greenhouse-Geisser	1032.67	3.44	300.58	162.65	.000	0.910	558.81	1.000
Time * CONDT * Group	Sphericity Assumed	10.00	7.00	1.43	1.58	.150	.090	11.03	.633
	Greenhouse-Geisser	10.00	3.44	2.91	1.58	.201	.090	5.41	.420
Error(Time*CONDT)	Sphericity Assumed	101.58	112.00	0.91					
	Greenhouse-Geisser	101.58	54.97	1.85					

a. Computed using alpha = .05, Mauchly's test indicated that the assumption of sphericity had been violated, $X^2(27) = 88.9$, P = .017, therefor degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity (.495).

Table 38

Pairwise Comparisons for Phsyiolgical Stain Index during Hyperthermia and Control Treatments

(I) Time	(J) Time	Mean Difference (I-J)	Std. Error	Sig.[a]	95% Confidence Lower Bound	95% Confidence Upper Bound
1	2	-0.361	0.190	1.000	-1.071	0.349
	3	-0.694	0.222	0.183	-1.526	0.137
	4	-1.722*	0.306	0.001	-2.865	-0.579
	5	-2.833*	0.336	0.000	-4.089	-1.578
	6	-3.333*	0.275	0.000	-4.362	-2.305
	7	-3.833*	0.257	0.000	-4.794	-2.873
	8	-4.500*	0.269	0.000	-5.505	-3.495

Table 39

RM ANOVA Main Effects for Phsyiolgical Stain Index during Recovery from Hyperthermia and Control Treatments

Source		Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared	Noncent. Parameter	Observed Power[a]
Time	Sphericity Assumed	532.89	7.00	76.13	39.35	.000	0.711	275.46	1.000
	Greenhouse-Geisser	532.89	2.76	192.88	39.35	.000	0.711	108.72	1.000
Time * Group	Sphericity Assumed	9.89	7.00	1.41	0.73	.647	0.044	5.11	0.302
	Greenhouse-Geisser	9.89	2.76	3.58	0.73	.529	0.044	2.02	0.187
Error(Time)	Sphericity Assumed	216.67	112.00	1.93					
	Greenhouse-Geisser	216.67	44.20	4.90					
CONDT	Sphericity Assumed	2250.09	1.00	2250.09	201.91	.000	0.927	201.91	1.000
	Greenhouse-Geisser	2250.09	1.00	2250.09	201.91	.000	0.927	201.91	1.000
CONDT * Group	Sphericity Assumed	103.92	1.00	103.92	9.33	.008	0.368	9.33	0.818
	Greenhouse-Geisser	103.92	1.00	103.92	9.33	.008	0.368	9.33	0.818
Error(CONDT)	Sphericity Assumed	178.31	16.00	11.14					
	Greenhouse-Geisser	178.31	16.00	11.14					
Time * CONDT	Sphericity Assumed	698.33	7.00	99.76	63.96	.000	0.800	447.71	1.000
	Greenhouse-Geisser	698.33	2.66	262.15	63.96	.000	0.800	170.38	1.000
Time * CONDT * Group	Sphericity Assumed	17.16	7.00	2.45	1.57	.151	.089	11.00	.632
	Greenhouse-Geisser	17.16	2.66	6.44	1.57	.214	.089	4.19	.362
Error(Time*CONDT)	Sphericity Assumed	174.69	112.00	1.56					
	Greenhouse-Geisser	174.69	42.62	4.10					

a. Computed using alpha = .05, Mauchly's test indicated that the assumption of sphericity had been violated, $X^2(27) = 67.27$, P = .000, therefor degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity (.395).

Table 40

Pairwise Comparisons forPhsyiolgical Stain Index during Recovery from Hyperthermia and Control Treatments

(I) Time	(J) Time	Mean Difference (I-J)	Std. Error	Sig.[a]	95% Confidence Lower Bound	95% Confidence Upper Bound
1	2	-4.250*	0.356	0.000	-5.580	-2.920
	3	-3.389*	0.324	0.000	-4.601	-2.176
	4	-2.500*	0.328	0.000	-3.727	-1.273
	5	-1.750*	0.358	0.005	-3.089	-0.411
	6	-0.889	0.371	0.812	-2.275	0.497
	7	-0.917	0.372	0.716	-2.309	0.476
	8	-0.833	0.407	1.000	-2.357	0.690

Table 41

RM ANOVA Main Effects for Systolic Blood Pressure during Hyperthermia and Control Treatments

Source		Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared	Noncent. Parameter	Observed Power[a]
Time	Sphericity Assumed	682.84	7.00	97.55	2.87	.008	0.144	20.07	0.911
Time * Group	Sphericity Assumed	91.17	7.00	13.02	0.38	.911	0.022	2.68	0.166
Error(Time)	Sphericity Assumed	4049.61	119.00	34.03					
CONDT	Sphericity Assumed	575.62	1.00	575.62	0.43	.520	0.025	0.43	0.095
CONDT * Group	Sphericity Assumed	79.68	1.00	79.68	0.06	.810	0.003	0.06	0.056
Error(CONDT)	Sphericity Assumed	22716.78	17.00	1336.28					
Time * CONDT	Sphericity Assumed	566.52	7.00	80.93	2.37	.027	0.122	16.58	0.839
Time * CONDT * Group	Sphericity Assumed	354.31	7.00	50.62	1.48	.180	.080	10.37	.603
Error(Time*CONDT)	Sphericity Assumed	4066.69	119.00	34.17					

a. Computed using alpha = .05

Table 42

Pairwise Comparisons for Systolic Blood Pressure during Hyperthermia and Control Treatments

(I) Time	(J) Time	Mean Difference (I-J)	Std. Error	Sig.[a]	95% Confidence Lower Bound	95% Confidence Upper Bound
1	2	1.822	1.269	1.000	-2.870	6.515
	3	3.224	1.306	0.686	-1.606	8.054
	4	1.706	1.366	1.000	-3.347	6.758
	5	-1.006	1.181	1.000	-5.373	3.362
	6	0.854	1.605	1.000	-5.081	6.789
	7	-0.363	1.586	1.000	-6.229	5.504
	8	-1.519	1.468	1.000	-6.949	3.910

Table 43

RM ANOVA Main Effects for Systolic Blood Pressure during Recovery from Hyperthermia and Control Treatments

Source		Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared	Noncent. Parameter	Observed Power[a]
Time	Sphericity Assumed	633.39	7.00	90.48	2.79	.010	0.141	19.50	0.902
Time * Group	Sphericity Assumed	192.92	7.00	27.56	0.85	.550	0.048	5.94	0.353
Error(Time)	Sphericity Assumed	3865.30	119.00	32.48					
CONDT	Sphericity Assumed	6887.58	1.00	6887.58	5.37	.033	0.240	5.37	0.589
CONDT * Group	Sphericity Assumed	16.33	1.00	16.33	0.01	.911	0.001	0.01	0.051
Error(CONDT)	Sphericity Assumed	21799.64	17.00	1282.33					
Time * CONDT	Sphericity Assumed	1362.79	7.00	194.68	4.02	.001	0.191	28.12	0.981
Time * CONDT * Group	Sphericity Assumed	420.80	7.00	60.11	1.24	.286	.068	8.68	.513
Error(Time*CONDT)	Sphericity Assumed	5767.05	119.00	48.46					

a. Computed using alpha = .05

Table 44

Pairwise Comparisons for Systolic Blood Pressure during Recovery from Hyperthermia and Control Treatments

(I) Time	(J) Time	Mean Difference (I-J)	Std. Error	Sig.[a]	95% Confidence Lower Bound	95% Confidence Upper Bound
1	2	3.858	1.715	1.000	-2.484	10.201
	3	1.651	1.262	1.000	-3.018	6.319
	4	3.389	1.678	1.000	-2.815	9.592
	5	1.111	1.334	1.000	-3.822	6.045
	6	-0.065	1.253	1.000	-4.700	4.570
	7	1.401	1.447	1.000	-3.950	6.753
	8	-0.169	1.078	1.000	-4.157	3.819

Table 45

RM ANOVA Main Effects for Diastolic Blood Pressure during Hyperthermia and Control Treatments

Source		Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared	Noncent. Parameter	Observed Power[a]
Time	Sphericity Assumed	3460.47	7.00	494.35	17.76	.000	0.511	124.29	1.000
	Greenhouse-Geisser	3460.47	3.28	1053.96	17.76	.000	0.511	58.30	1.000
Time * Group	Sphericity Assumed	111.94	7.00	15.99	0.57	.776	0.033	4.02	0.240
	Greenhouse-Geisser	111.94	3.28	34.09	0.57	.649	0.033	1.89	0.167
Error(Time)	Sphericity Assumed	3313.24	119.00	27.84					
	Greenhouse-Geisser	3313.24	55.82	59.36					
CONDT	Sphericity Assumed	26699.83	1.00	26699.83	34.69	.000	0.671	34.69	1.000
	Greenhouse-Geisser	26699.83	1.00	26699.83	34.69	.000	0.671	34.69	1.000
CONDT * Group	Sphericity Assumed	0.49	1.00	0.49	0.00	.980	0.000	0.00	0.050
	Greenhouse-Geisser	0.49	1.00	0.49	0.00	.980	0.000	0.00	0.050
Error(CONDT)	Sphericity Assumed	13083.72	17.00	769.63					
	Greenhouse-Geisser	13083.72	17.00	769.63					
Time * CONDT	Sphericity Assumed	4442.54	7.00	634.65	22.49	.000	0.569	157.40	1.000
	Greenhouse-Geisser	4442.54	4.38	1014.48	22.49	.000	0.569	98.47	1.000
Time * CONDT * Group	Sphericity Assumed	190.01	7.00	27.14	0.96	.462	.054	6.73	.400
	Greenhouse-Geisser	190.01	4.38	43.39	0.96	.439	.054	4.21	.304
Error(Time*CONDT)	Sphericity Assumed	3358.78	119.00	28.23					
	Greenhouse-Geisser	3358.78	74.45	45.12					

a. Computed using alpha = .05, Mauchly's test indicated that the assumption of sphericity had been violated, $X^2(27) = 64.24$, P = .000, therefor degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity (.469).

Table 46

Pairwise Comparisons for Diastolic Blood Pressure during Hyperthermia and Control Treatments

(I) Time	(J) Time	Mean Difference (I-J)	Std. Error	Sig.[a]	95% Confidence Lower Bound	95% Confidence Upper Bound
1	2	5.421*	1.126	0.005	1.258	9.584
	3	6.882*	1.208	0.001	2.415	11.350
	4	7.524*	1.116	0.000	3.399	11.649
	5	8.563*	1.483	0.001	3.079	14.046
	6	10.966*	1.823	0.000	4.224	17.707
	7	10.113*	1.284	0.000	5.363	14.863
	8	10.725*	1.285	0.000	5.974	15.476

Table 47

RM ANOVA Main Effects for Diastolic Blood Pressure during Recovery from Hyperthermia and Control Treatments

Source		Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared	Noncent. Parameter	Observed Power[a]
Time	Sphericity Assumed	2178.43	7.00	311.20	11.38	.000	0.401	79.64	1.000
Time * Group	Sphericity Assumed	265.69	7.00	37.96	1.39	.217	0.075	9.71	0.569
Error(Time)	Sphericity Assumed	3255.03	119.00	27.35					
CONDT	Sphericity Assumed	8686.83	1.00	8686.83	12.51	.003	0.424	12.51	0.915
CONDT * Group	Sphericity Assumed	107.05	1.00	107.05	0.15	.699	0.009	0.15	0.066
Error(CONDT)	Sphericity Assumed	11803.41	17.00	694.32					
Time * CONDT	Sphericity Assumed	2654.99	7.00	379.28	13.62	.000	0.445	95.36	1.000
Time * CONDT * Group	Sphericity Assumed	159.00	7.00	22.71	0.82	.576	.046	5.71	.339
Error(Time*CONDT)	Sphericity Assumed	3313.04	119.00	27.84					

a. Computed using alpha = .05

Table 48

Pairwise Comparisons for Diastolic Blood Pressure during Recovery from Hyperthermia and Control Treatments

(I) Time	(J) Time	Mean Difference (I-J)	Std. Error	Sig.[a]	95% Confidence Lower Bound	95% Confidence Upper Bound
1	2	7.957*	1.446	0.001	2.610	13.304
	3	6.594*	1.336	0.004	1.653	11.535
	4	4.197	1.177	0.067	-0.155	8.549
	5	1.998	1.280	1.000	-2.737	6.732
	6	1.773	0.895	1.000	-1.535	5.081
	7	2.695	1.106	0.732	-1.396	6.786
	8	0.307	1.049	1.000	-3.571	4.186

Table 49

RM ANOVA Main Effects for Mean Arterial Blood Pressure during Hyperthermia and Control Treatments

Source		Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared	Noncent. Parameter	Observed Power[a]
Time	Sphericity Assumed	1334.54	7.00	190.65	9.75	.000	0.364	68.23	1.000
	Greenhouse-Geisser	1334.54	3.87	344.54	9.75	.000	0.364	37.75	0.999
Time * Group	Sphericity Assumed	61.44	7.00	8.78	0.45	.869	0.026	3.14	0.191
	Greenhouse-Geisser	61.44	3.87	15.86	0.45	.767	0.026	1.74	0.147
Error(Time)	Sphericity Assumed	2327.68	119.00	19.56					
	Greenhouse-Geisser	2327.68	65.85	35.35					
CONDT	Sphericity Assumed	13653.37	1.00	13653.37	19.23	.000	0.531	19.23	0.985
	Greenhouse-Geisser	13653.37	1.00	13653.37	19.23	.000	0.531	19.23	0.985
CONDT * Group	Sphericity Assumed	11.12	1.00	11.12	0.02	.902	0.001	0.02	0.052
	Greenhouse-Geisser	11.12	1.00	11.12	0.02	.902	0.001	0.02	0.052
Error(CONDT)	Sphericity Assumed	12072.17	17.00	710.13					
	Greenhouse-Geisser	12072.17	17.00	710.13					
Time * CONDT	Sphericity Assumed	2308.82	7.00	329.83	17.58	.000	0.508	123.04	1.000
	Greenhouse-Geisser	2308.82	4.67	494.15	17.58	.000	0.508	82.13	1.000
Time * CONDT * Group	Sphericity Assumed	132.36	7.00	18.91	1.01	.429	.056	7.05	.419
	Greenhouse-Geisser	132.36	4.67	28.33	1.01	.416	.056	4.71	.330
Error(Time*CONDT)	Sphericity Assumed	2232.95	119.00	18.76					
	Greenhouse-Geisser	2232.95	79.43	28.11					

a. Computed using alpha = .05, Mauchly's test indicated that the assumption of sphericity had been violated, $X^2(27) = 43.1$, P = .030, therefor degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity (.553).

Table 50

Pairwise Comparisons for Mean Arterial Blood Pressure during Hyperthermia and Control Treatments

(I) Time	(J) Time	Mean Difference (I-J)	Std. Error	Sig.[a]	95% Confidence Lower Bound	95% Confidence Upper Bound
1	2	4.053*	1.032	0.030	0.236	7.871
	3	5.389*	1.073	0.003	1.422	9.357
	4	5.308*	0.943	0.001	1.819	8.796
	5	5.102*	1.109	0.007	1.003	9.201
	6	7.317*	1.461	0.003	1.914	12.721
	7	6.351*	1.051	0.000	2.463	10.238
	8	6.368*	1.186	0.001	1.984	10.753

Table 51

RM ANOVA Main Effects for Mean Arterial Blood Pressure during Recovery from Hyperthermia and Control Treatments

Source		Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared	Noncent. Parameter	Observed Power[a]
Time	Sphericity Assumed	1464.99	7.00	209.28	9.86	.000	0.367	69.04	1.000
	Greenhouse-Geisser	1464.99	3.39	432.32	9.86	.000	0.367	33.42	0.998
Time * Group	Sphericity Assumed	145.20	7.00	20.74	0.98	.451	0.054	6.84	0.407
	Greenhouse-Geisser	145.20	3.39	42.85	0.98	.417	0.054	3.31	0.268
Error(Time)	Sphericity Assumed	2525.11	119.00	21.22					
	Greenhouse-Geisser	2525.11	57.61	43.83					
CONDT	Sphericity Assumed	8009.31	1.00	8009.31	13.34	.002	0.440	13.34	0.931
	Greenhouse-Geisser	8009.31	1.00	8009.31	13.34	.002	0.440	13.34	0.931
CONDT * Group	Sphericity Assumed	65.90	1.00	65.90	0.11	.744	0.006	0.11	0.061
	Greenhouse-Geisser	65.90	1.00	65.90	0.11	.744	0.006	0.11	0.061
Error(CONDT)	Sphericity Assumed	10204.34	17.00	600.26					
	Greenhouse-Geisser	10204.34	17.00	600.26					
Time * CONDT	Sphericity Assumed	1856.05	7.00	265.15	11.76	.000	0.409	82.30	1.000
	Greenhouse-Geisser	1856.05	2.96	627.49	11.76	.000	0.409	34.78	0.999
Time * CONDT * Group	Sphericity Assumed	178.08	7.00	25.44	1.13	.350	.062	7.90	.469
	Greenhouse-Geisser	178.08	2.96	60.21	1.13	.346	.062	3.34	.284
Error(Time*CONDT)	Sphericity Assumed	2683.74	119.00	22.55					
	Greenhouse-Geisser	2683.74	50.28	53.37					

a. Computed using alpha = .05, Mauchly's test indicated that the assumption of sphericity had been violated, $X^2(27) = 48.6$, P = .008, therefor degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity (.553).

Table 52

Pairwise Comparisons for Mean Arterial Blood Pressure during Recovery from Hyperthermia and Control Treatments

(I) Time	(J) Time	Mean Difference (I-J)	Std. Error	Sig.[a]	95% Confidence Lower Bound	95% Confidence Upper Bound
1	2	6.312*	1.279	0.004	1.581	11.043
	3	4.673*	1.132	0.020	0.488	8.859
	4	3.659	1.191	0.194	-0.746	8.063
	5	1.431	1.095	1.000	-2.619	5.481
	6	0.891	0.842	1.000	-2.224	4.006
	7	1.989	1.018	1.000	-1.777	5.755
	8	-0.339	0.840	1.000	-3.444	2.766

Table 53

RM ANOVA Main Effects for Plasma Glucose during a 75 g Oral Glucose Tolerane Test Post Hyperthermia and Control Treatments

Source		Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared	Noncent. Parameter	Observed Power[a]
Time	Sphericity Assumed	172328.29	5.00	34465.66	47.21	.000	0.747	236.03	1.000
	Greenhouse-Geisser	172328.29	2.34	73766.35	47.21	.000	0.747	110.28	1.000
Time * Group	Sphericity Assumed	96735.70	5.00	19347.14	26.50	.000	0.624	132.49	1.000
	Greenhouse-Geisser	96735.70	2.34	41408.40	26.50	.000	0.624	61.90	1.000
Error(Time)	Sphericity Assumed	58409.11	80.00	730.11					
	Greenhouse-Geisser	58409.11	37.38	1562.65					
CONDT	Sphericity Assumed	177.13	1.00	177.13	0.19	.669	0.012	0.19	0.069
	Greenhouse-Geisser	177.13	1.00	177.13	0.19	.669	0.012	0.19	0.069
CONDT * Group	Sphericity Assumed	2153.35	1.00	2153.35	2.30	.149	0.126	2.30	0.297
	Greenhouse-Geisser	2153.35	1.00	2153.35	2.30	.149	0.126	2.30	0.297
Error(CONDT)	Sphericity Assumed	14963.44	16.00	935.22					
	Greenhouse-Geisser	14963.44	16.00	935.22					
Time * CONDT	Sphericity Assumed	1428.40	5.00	285.68	2.09	.075	0.116	10.46	0.666
	Greenhouse-Geisser	1428.40	2.97	480.68	2.09	.114	0.116	6.22	0.500
Time * CONDT * Group	Sphericity Assumed	880.32	5.00	176.06	1.29	.277	.075	6.45	.435
	Greenhouse-Geisser	880.32	2.97	296.24	1.29	.289	.075	3.83	.321
Error(Time*CONDT)	Sphericity Assumed	10920.53	80.00	136.51					
	Greenhouse-Geisser	10920.53	47.55	229.68					

a. Computed using alpha = .05, Mauchly's test indicated that the assumption of sphericity had been violated, $X^2(27) = 58.81$, P = .000, therefor degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity (.467).

Table 54

Pairwise Comparisons for Plasma Glucose during a 75 g Oral Glucose Tolerane Test Post Hyperthermia and Control Treatments

(I) Time	(J) Time	Mean Difference (I-J)	Std. Error	Sig.[a]	95% Confidence Lower Bound	95% Confidence Upper Bound
1	2	-14.178*	2.091	0.000	-21.380	-6.976
	3	-54.288*	5.147	0.000	-72.016	-36.559
	4	-70.978*	7.429	0.000	-96.565	-45.391
	5	-71.861*	6.370	0.000	-93.801	-49.921
	6	-63.240*	7.629	0.000	-89.518	-36.963

Table 55

RM ANOVA Main Effects for Plasma C-Peptide during a 75 g Oral Glucose Tolerane Test Post Hyperthermia and Control Treatments

Source		Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared	Noncent. Parameter	Observed Power[a]
Time	Sphericity Assumed	140773.59	5.00	28154.72	53.27	.000	0.769	266.37	1.000
	Greenhouse-Geisser	140773.59	1.86	75869.85	53.27	.000	0.769	98.85	1.000
Time * Group	Sphericity Assumed	7598.18	5.00	1519.64	2.88	.019	0.152	14.38	0.820
	Greenhouse-Geisser	7598.18	1.86	4095.04	2.88	.076	0.152	5.34	0.502
Error(Time)	Sphericity Assumed	42278.63	80.00	528.48					
	Greenhouse-Geisser	42278.63	29.69	1424.13					
CONDT	Sphericity Assumed	11.96	1.00	11.96	0.01	.912	0.001	0.01	0.051
	Greenhouse-Geisser	11.96	1.00	11.96	0.01	.912	0.001	0.01	0.051
CONDT * Group	Sphericity Assumed	0.98	1.00	0.98	0.00	.975	0.000	0.00	0.050
	Greenhouse-Geisser	0.98	1.00	0.98	0.00	.975	0.000	0.00	0.050
Error(CONDT)	Sphericity Assumed	15228.30	16.00	951.77					
	Greenhouse-Geisser	15228.30	16.00	951.77					
Time * CONDT	Sphericity Assumed	1871.98	5.00	374.40	2.70	.026	0.145	13.52	0.793
	Greenhouse-Geisser	1871.98	3.54	529.19	2.70	.045	0.145	9.57	0.677
Time * CONDT * Group	Sphericity Assumed	183.71	5.00	36.74	0.27	.931	.016	1.33	.112
	Greenhouse-Geisser	183.71	3.54	51.93	0.27	.879	.016	0.94	.101
Error(Time*CONDT)	Sphericity Assumed	11073.98	80.00	138.42					
	Greenhouse-Geisser	11073.98	56.60	195.66					

a. Computed using alpha = .05, Mauchly's test indicated that the assumption of sphericity had been violated, $X^2(54.3) = 14$, p = .000, therefor degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity (.371).

Table 56

Pairwise Comparisons for Plasma C-Peptide during a 75 g Oral Glucose Tolerane Test Post Hyperthermia and Control Treatments

(I) Time	(J) Time	Mean Difference (I-J)	Std. Error	Sig.[a]	95% Confidence Lower Bound	95% Confidence Upper Bound
1	2	-12.752*	2.951	0.008	-22.916	-2.589
	3	-39.725*	3.995	0.000	-53.487	-25.964
	4	-58.961*	5.564	0.000	-78.125	-39.797
	5	-60.970*	5.893	0.000	-81.268	-40.672
	6	-67.724*	7.099	0.000	-92.176	-43.272

Table 57

RM ANOVA Main Effects for Plasma Insulin during a 75 g Oral Glucose Tolerane Test Post Hyperthermia and Control Treatments

Source		Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared	Noncent. Parameter	Observed Power[a]
Time	Sphericity Assumed	24259.85	5.00	4851.97	23.49	.000	0.595	117.47	1.000
	Greenhouse-Geisser	24259.85	2.25	10795.88	23.49	.000	0.595	52.80	1.000
Time * Group	Sphericity Assumed	2826.77	5.00	565.35	2.74	.025	0.146	13.69	0.798
	Greenhouse-Geisser	2826.77	2.25	1257.94	2.74	.072	0.146	6.15	0.536
Error(Time)	Sphericity Assumed	16521.11	80.00	206.51					
	Greenhouse-Geisser	16521.11	35.95	459.50					
CONDT	Sphericity Assumed	47.02	1.00	47.02	0.18	.673	0.011	0.18	0.069
	Greenhouse-Geisser	47.02	1.00	47.02	0.18	.673	0.011	0.18	0.069
CONDT * Group	Sphericity Assumed	1.37	1.00	1.37	0.01	.942	0.000	0.01	0.051
	Greenhouse-Geisser	1.37	1.00	1.37	0.01	.942	0.000	0.01	0.051
Error(CONDT)	Sphericity Assumed	4067.35	16.00	254.21					
	Greenhouse-Geisser	4067.35	16.00	254.21					
Time * CONDT	Sphericity Assumed	374.95	5.00	74.99	1.49	.204	0.085	7.43	0.496
	Greenhouse-Geisser	374.95	2.06	182.35	1.49	.241	0.085	3.05	0.298
Time * CONDT * Group	Sphericity Assumed	145.21	5.00	29.04	0.58	.719	.035	2.88	.201
	Greenhouse-Geisser	145.21	2.06	70.62	0.58	.573	.035	1.18	.138
Error(Time*CONDT)	Sphericity Assumed	4039.23	80.00	50.49					
	Greenhouse-Geisser	4039.23	32.90	122.78					

a. Computed using alpha = .05, Mauchly's test indicated that the assumption of sphericity had been violated, X2(27) = 67.8, P = .000, therefor degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity (.449).

Table 58

Pairwise Comparisons for Plasma Insulin during a 75 g Oral Glucose Tolerane Test Post Hyperthermia and Control Treatments

(I) Time	(J) Time	Mean Difference (I-J)	Std. Error	Sig.[a]	95% Confidence Lower Bound	95% Confidence Upper Bound
1	2	-6.293*	0.957	0.000	-9.587	-2.998
	3	-21.535*	3.332	0.000	-33.013	-10.058
	4	-25.776*	3.763	0.000	-38.736	-12.817
	5	-25.884*	3.389	0.000	-37.557	-14.211
	6	-26.841*	3.714	0.000	-39.633	-14.049

Table 59

RM ANOVA Main Effects for Mean Plasma Leptin during a 75 g Oral Glucose Tolerane Test Post Hyperthermia and Control Treatments

Source		Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared	Noncent. Parameter	Observed Power[a]
Time	Sphericity Assumed	33166134.71	1.00	33166134.71	6.46	.024	0.316	6.46	0.657
Time * Group	Sphericity Assumed	10732541.40	1.00	10732541.40	2.09	.170	0.130	2.09	0.270
Error(Time)	Sphericity Assumed	71927456.80	14.00	5137675.49					

a. Computed using alpha = .05

Table 60

Pairwise Comparisons for Mean Plasma Leptin during a 75 g Oral Glucose Tolerane Test Post Hyperthermia and Control Treatments

(I) Time	(J) Time	Mean Difference (I-J)	Std. Error	Sig.[a]	95% Confidence Lower Bound	95% Confidence Upper Bound
1	2	-2036.116*	801.380	0.024	-3,754.904	-317.327
2	1	2036.116*	801.380	0.024	317.327	3,754.904

Table 61

RM ANOVA Main Effects for Plasma Glucose Area Under the Curve during a 75 g Oral Glucose Tolerane Test Post Hyperthermia and Control Treatments

Source		Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared	Noncent. Parameter	Observed Power[a]
Time	Sphericity Assumed	321417.18	1.00	321417.18	0.12	.731	0.008	0.12	0.063
Time * Group	Sphericity Assumed	4839721.34	1.00	4839721.34	1.84	.194	0.103	1.84	0.248
Error(Time)	Sphericity Assumed	42043674.71	16.00	2627729.67					

a. Computed using alpha = .05

Table 62

Pairwise Comparisons for Plasma Glucose Area Under the Curve during a 75 g Oral Glucose Tolerane Test Post Hyperthermia and Control

(I) Time	(J) Time	Mean Difference (I-J)	Std. Error	Sig.[a]	95% Confidence Lower Bound	95% Confidence Upper Bound
1	2	188.979	540.342	0.731	-956.496	1,334.454
2	1	-188.979	540.342	0.731	-1,334.454	956.496

Table 63

RM ANOVA Main Effects for Plasma C-Peptide Area Under the Curve during a 75 g Oral Glucose Tolerane Test Post Hyperthermia and Control Treatments

Source		Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared	Noncent. Parameter	Observed Power[a]
Time	Sphericity Assumed	163507.01	1.00	163507.01	0.06	.805	0.004	0.06	0.056
Time * Group	Sphericity Assumed	552.25	1.00	552.25	0.00	.989	0.000	0.00	0.050
Error(Time)	Sphericity Assumed	41432178.36	16.00	2589511.15					

a. Computed using alpha = .05

Table 64

Pairwise Comparisons for Plasma C-Peptide Area Under the Curve during a 75 g Oral Glucose Tolerane Test Post Hyperthermia and Control

(I) Time	(J) Time	Mean Difference (I-J)	Std. Error	Sig.[a]	95% Confidence Lower Bound	95% Confidence Upper Bound
1	2	134.787	536.399	0.805	-1,002.328	1,271.901
2	1	-134.787	536.399	0.805	-1,271.901	1,002.328

Table 65

RM ANOVA Main Effects for Plasma C-Peptide Area Under the Curve during a 75 g Oral Glucose Tolerane Test Post Hyperthermia and Control Treatments

Source		Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared	Noncent. Parameter	Observed Power[a]
Time	Sphericity Assumed	377882.73	1.00	377882.73	0.35	.562	0.021	0.35	0.086
Time * Group	Sphericity Assumed	127483.51	1.00	127483.51	0.12	.735	0.007	0.12	0.062
Error(Time)	Sphericity Assumed	17209033.24	16.00	1075564.58					

a. Computed using alpha = .05

Table 66

Pairwise Comparisons for Plasma C-Peptide Area Under the Curve during a 75 g Oral Glucose Tolerane Test Post Hyperthermia and Control

(I) Time	(J) Time	Mean Difference (I-J)	Std. Error	Sig.[a]	95% Confidence Lower Bound	95% Confidence Upper Bound
1	2	-204.907	345.698	0.562	-937.754	527.940
2	1	204.907	345.698	0.562	-527.940	937.754

APPENDIX I

Independent T Test Tables

Independent Samples Test for Type 2 Diabetics and Healthy Controls

		Levene's Test		t-test for Equality of Means						
									95% Confidence Interval	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
kg	Equal variances assumed	2.735	0.119	3.885	15.000	0.001	39.826	10.251	17.976	61.677
	Equal variances not assumed			3.719	9.223	0.005	39.826	10.709	15.690	63.963
ht	Equal variances assumed	0.045	0.834	-0.534	15.000	0.601	-2.443	4.575	-12.194	7.308
	Equal variances not assumed			-0.529	13.899	0.605	-2.443	4.620	-12.359	7.473
waist	Equal variances assumed	0.016	0.900	6.640	15.000	0.000	32.042	4.825	21.757	42.327
	Equal variances not assumed			6.614	14.478	0.000	32.042	4.845	21.683	42.401
age	Equal variances assumed	0.185	0.673	1.765	15.000	0.098	10.353	5.865	-2.149	22.855
	Equal variances not assumed			1.781	14.994	0.095	10.353	5.812	-2.036	22.742
a1c	Equal variances assumed	0.148	0.706	4.823	15.000	0.000	1.368	0.284	0.763	1.973
	Equal variances not assumed			4.802	14.438	0.000	1.368	0.285	0.759	1.977
BSA	Equal variances assumed	0.499	0.491	2.238	15.000	0.041	0.288	0.128	0.014	0.561
	Equal variances not assumed			2.176	11.431	0.051	0.288	0.132	-0.002	0.577
BMI	Equal variances assumed	0.304	0.590	6.106	15.000	0.000	16.060	2.630	10.454	21.666
	Equal variances not assumed			5.937	11.411	0.000	16.060	2.705	10.132	21.988
Fatmass	Equal variances assumed	4.435	0.052	4.028	15.000	0.001	34.947	8.676	16.454	53.441
	Equal variances not assumed			3.840	8.700	0.004	34.947	9.101	14.251	55.644
Leanmass	Equal variances assumed	0.002	0.963	1.037	15.000	0.316	11.214	10.818	-11.844	34.272
	Equal variances not assumed			1.042	14.969	0.314	11.214	10.764	-11.733	34.161
percentfat	Equal variances assumed	1.689	0.213	4.076	15.000	0.001	12.749	3.128	6.082	19.415
	Equal variances not assumed			4.206	13.014	0.001	12.749	3.031	6.201	19.296
gynoidfat	Equal variances assumed	0.922	0.352	2.490	15.000	0.025	9.326	3.746	1.342	17.311
	Equal variances not assumed			2.537	14.531	0.023	9.326	3.676	1.469	17.184
androidfat	Equal variances assumed	4.167	0.059	4.755	15.000	0.000	16.247	3.417	8.965	23.530
	Equal variances not assumed			5.003	9.832	0.001	16.247	3.248	8.994	23.500

Independent Samples Test for Type 2 Diabetics and Healthy Controls

		for Equality		t-test for Equality of Means						
									of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
fastinsulin	Equal variances assumed	2.478	0.136	5.052	15.000	0.000	10.386	2.056	6.005	14.768
	Equal variances not assumed			4.866	10.036	0.001	10.386	2.135	5.632	15.140
glucose2h	Equal variances assumed	4.363	0.054	5.750	15.000	0.000	135.593	23.583	85.327	185.859
	Equal variances not assumed			5.604	11.767	0.000	135.593	24.196	82.758	188.428
cholesterol	Equal variances assumed	2.530	0.133	0.768	15.000	0.454	13.528	17.605	-23.997	51.053
	Equal variances not assumed			0.737	9.547	0.479	13.528	18.347	-27.615	54.671
triglyceride	Equal variances assumed	0.032	0.861	4.665	15.000	0.000	98.660	21.148	53.583	143.736
	Equal variances not assumed			4.658	14.663	0.000	98.660	21.183	53.420	143.900
HDL	Equal variances assumed	0.595	0.453	-4.526	15.000	0.000	-22.614	4.996	-33.263	-11.965
	Equal variances not assumed			-4.665	13.208	0.000	-22.614	4.848	-33.070	-12.157
LDL	Equal variances assumed	4.827	0.044	1.201	15.000	0.248	19.165	15.957	-14.846	53.176
	Equal variances not assumed			1.140	8.216	0.286	19.165	16.805	-19.409	57.740
BMD	Equal variances assumed	1.385	0.258	2.691	15.000	0.017	0.186	0.069	0.039	0.334
	Equal variances not assumed			2.633	12.361	0.021	0.186	0.071	0.033	0.340
glu0	Equal variances assumed	37.479	0.000	3.742	15.000	0.002	48.757	13.030	20.984	76.530
	Equal variances not assumed			3.534	7.601	0.008	48.757	13.798	16.647	80.867
glu120	Equal variances assumed	5.279	0.036	5.369	15.000	0.000	140.557	26.178	84.761	196.353
	Equal variances not assumed			5.155	9.609	0.000	140.557	27.267	79.466	201.648
ins0	Equal variances assumed	1.607	0.224	3.695	15.000	0.002	10.462	2.832	4.427	16.498
	Equal variances not assumed			3.590	11.312	0.004	10.462	2.914	4.070	16.855
ins120	Equal variances assumed	0.663	0.428	2.928	15.000	0.010	21.182	7.235	5.760	36.603
	Equal variances not assumed			2.957	14.981	0.010	21.182	7.163	5.912	36.451
cpep0	Equal variances assumed	2.220	0.157	2.697	15.000	0.017	34.396	12.754	7.211	61.580
	Equal variances not assumed			2.626	11.634	0.023	34.396	13.098	5.759	63.033
cpep120	Equal variances assumed	3.577	0.078	2.660	15.000	0.018	38.245	14.380	7.594	68.895
	Equal variances not assumed			2.739	13.311	0.017	38.245	13.964	8.150	68.340
lept0	Equal variances assumed	0.343	0.567	2.202	15.000	0.044	8626.736	3918.362	274.946	16978.527
	Equal variances not assumed			2.197	14.634	0.045	8626.736	3926.357	239.636	17013.836
lept120	Equal variances assumed	0.355	0.560	2.022	15.000	0.061	8620.660	4262.446	-464.528	17705.848
	Equal variances not assumed			2.009	14.225	0.064	8620.660	4291.580	-570.244	17811.563
AUCglucose	Equal variances assumed	2.349	0.146	5.890	15.000	0.000	13400.289	2275.095	8551.040	18249.539
	Equal variances not assumed			5.698	10.690	0.000	13400.289	2351.566	8206.141	18594.438
AUCinsulin	Equal variances assumed	0.235	0.635	0.982	15.000	0.341	836.638	851.576	-978.454	2651.730
	Equal variances not assumed			1.017	12.568	0.328	836.638	822.837	-947.225	2620.501
AUCcpeptide	Equal variances assumed	0.629	0.440	1.652	15.000	0.119	2420.967	1465.289	-702.223	5544.157
	Equal variances not assumed			1.666	14.999	0.116	2420.967	1453.238	-676.549	5518.483
AUCleptin	Equal variances assumed	0.268	0.613	2.175	15.000	0.046	1065425.833	489881.769	21267.560	2109584.107
	Equal variances not assumed			2.168	14.547	0.047	1065425.833	491447.689	15083.523	2115768.143

Independent Samples Test for Type 2 Diabetics and Healthy Controls

		for Equality		t-test for Equality of Means						
									of the Difference	
		F	Sig	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
weightpre	Equal variances assumed	5.883	0.028	4.022	15.000	0.001	39.651	9.859	18.636	60.666
	Equal variances not assumed			3.803	7.735	0.006	39.651	10.427	15.461	63.841
wieghtpost	Equal variances assumed	5.911	0.028	4.087	15.000	0.001	40.131	9.820	19.201	61.060
	Equal variances not assumed			3.863	7.710	0.005	40.131	10.388	16.019	64.242
Sweatrate	Equal variances assumed	1.920	0.186	-0.252	15.000	0.804	-0.035	0.138	-0.328	0.259
	Equal variances not assumed			-0.264	10.371	0.797	-0.035	0.131	-0.326	0.256
Sweatrate(kg)	Equal variances assumed	2.555	0.131	-0.732	15.000	0.475	-0.064	0.087	-0.250	0.122
	Equal variances not assumed			-0.771	9.574	0.459	-0.064	0.083	-0.250	0.122
Temp	Equal variances assumed	2.135	0.165	-1.204	15.000	0.247	-0.590	0.490	-1.635	0.455
	Equal variances not assumed			-1.249	12.174	0.235	-0.590	0.472	-1.618	0.438
Humidity	Equal variances assumed	8.682	0.010	1.041	15.000	0.314	0.036	0.034	-0.037	0.109
	Equal variances not assumed			1.102	8.880	0.300	0.036	0.032	-0.038	0.109

APPENDIX J

Raw Data Tables

Descriptive Characteristics of the Participants

Type 2 Diabetics

ID	wt (kg)	ht (cm)	WC	Age	A1C (%)	FG (mg/dl)	Chol.	Trigly.	HDL	LDL	fat (%)	Tissue (kg)	Fat (kg)	Lean (kg)	FatFre e (kg)	Android (%fat)	Gynoid (%Fat)	BMD (g/cm)	BMI	BSA (m2)
DA	97.2	173.0	108.0	38.5	11.8	254.0	278.0	250.0	42.0	186.0	31.9	94.3	30.1	64.2	67.9	42.7	27.4	1.5	32.2	2.1
EB	112.0	167.1	119.6	49.3	7.3	151.1	192.6	180.9	36.4	120.1	45.7	122.8	57.2	65.6	68.9	52.6	45.1	1.4	40.5	2.2
HD	95.6	167.0	119.0	35.8	6.8	173.0	154.0	215.0	39.0	72.0	45.1	95.4	43.0	52.3	55.2	49.1	43.9	1.4	35.6	2.0
JC	141.7	183.0	136.0	65.0	6.8	108.0	160.0	139.0	33.0	99.0	40.8	135.2	55.2	80.0	84.0	52.5	36.6	1.6	44.1	2.6
LA	71.2	146.0	100.0	34.0	7.5	158.0	172.0	236.0	33.0	92.0	46.6	69.8	32.5	37.3	39.4	52.9	48.7	1.2	34.4	1.6
MC	101.3	163.0	123.0	56.0	6.0	104.0	208.0	92.0	49.0	141.0	50.1	217.2	108.7	108.5	113.9	57.8	48.7	1.2	40.5	2.1
SH	114.7	166.0	128.0	56.0	7.2	136.0	167.0	164.0	34.0	100.0	45.4	110.3	50.1	60.2	63.4	53.2	45.8	1.6	41.9	2.2
SK	111.0	167.5	119.0	56.7	6.1	108.0	281.0	179.0	38.0	207.0	50.0	109.3	54.6	54.7	57.5	54.3	51.0	1.4	39.4	2.2
SM	163.2	170.9	124.0	59.0	7.6	168.0	121.0	172.0	23.0	64.0	56.0	150.9	83.7	67.2	69.8	58.2	58.9	1.2	55.9	2.6
MEAN	112.0	167.1	119.6	50.0	7.5	151.1	192.6	180.9	36.4	120.1	45.7	122.8	57.2	65.6	68.9	52.6	45.1	1.4	40.5	2.2
SD	26.9	9.8	10.5	11.3	1.7	46.9	54.9	48.7	7.1	49.3	6.7	42.7	24.9	19.9	20.8	4.6	8.9	0.2	6.9	0.3
Non-Diabetics Controls																				
AL	72.8	166.0	83.0	25.9	5.5	95.5	142.0	40.0	54.0	72.0	38.6	74.8	28.9	45.9	49.0	36.0	45.1	1.3	29.0	1.8
CJ	73.4	180.5	84.5	37.2	4.9	92.0	142.0	176.0	31.0	76.0	20.5	71.7	14.7	57.0	59.9	20.9	22.3	1.2	22.8	1.9
CR	99.9	176.0	109.0	28.7	5.3	94.3	170.0	40.0	59.0	96.5	47.4	97.4	46.1	113.0	51.3	53.2	49.5	1.2	32.5	2.2
DT	61.8	167.0	83.8	61.9	5.3	90.6	168.4	73.6	58.3	96.5	36.7	60.5	22.2	38.3	40.3	42.7	42.3	1.0	22.6	1.7
EG	78.8	170.0	97.0	48.0	4.8	76.0	176.0	40.0	69.0	87.0	32.9	77.1	25.4	51.7	54.5	32.4	39.2	1.2	27.3	1.9
MH	79.7	178.5	89.0	36.2	5.1	98.6	194.0	80.0	65.0	113.0	27.8	80.1	22.3	57.7	60.9	33.7	27.0	1.3	27.1	2.0
MS	66.5	156.8	86.0	41.1	5.6	77.0	150.0	49.0	55.0	85.0	32.1	68.8	22.1	46.7	49.4	34.9	34.7	1.3	24.8	1.7
MT	59.5	168.0	76.0	31.8	5.9	86.4	205.0	90.0	75.0	112.0	32.9	57.9	19.1	38.9	41.1	37.9	39.1	1.2	21.0	1.7
TS	73.7	156.0	93.0	59.3	5.3	105.0	168.4	73.6	58.3	96.5	42.3	71.8	30.3	41.4	43.3	46.5	42.9	1.0	30.2	1.7
MEAN	74.0	168.8	89.0	41.1	5.3	90.6	168.4	73.6	58.3	92.7	34.6	73.3	25.7	54.5	50.0	37.6	38.0	1.2	26.4	1.8
SD	12.0	8.7	9.6	12.9	0.3	9.5	21.8	43.0	12.3	14.3	7.9	11.6	9.0	23.1	7.6	9.2	8.7	0.1	3.9	0.2

Note. ID = identification number, Ht = height, Wt = weight, BMI = body mass index, WC = waist circumference, Chol.= cholesterol, HDL = high density lipoprotein, LDL = low density lipoprotein, A1C = hemoglobin A1C, BMD = bone mineral density, BSA = body surface area, SD = standard deviation

Glucose Concentration (mg/dL) during a 75 g Oral Glucose Tolerance Test After Hyperthermia and Control Conditions

Type 2 Diabetics		Hyperthemia Condition						Control Condition					
ID	Time (min)	0	15	30	60	90	120	0	15	30	60	90	120
DA		272.0	281.5	349.0	407.0	428.5	425.0	264.0	307.0	358.0	404.0	406.0	412.5
EB		103.0	113.0	113.0	192.5	217.0	238.0	95.7	141.0	141.0	192.5	195.5	190.5
HD		142.0	161.0	235.5	266.0	316.5	332.0	179.5	209.0	254.5	312.0	316.0	284.0
JC		106.0	135.5	209.5	263.0	232.0	207.5	104.0	121.5	207.0	271.5	240.5	189.0
LA		161.0	174.0	206.5	263.0	298.0	312.5	191.0	226.5	270.5	327.5	363.5	383.0
MC		117.0	144.0	189.0	227.0	234.0	185.5	112.5	132.0	176.5	217.5	212.5	180.5
SH		138.5	157.5	227.0	264.5	228.5	206.5	150.0	177.0	239.5	273.5	234.0	202.5
SK		120.0	129.5	185.5	205.0	205.0	209.5	112.5	113.5	163.0	199.5	210.0	211.0
SM		170.0	182.5	209.5	252.0	288.5	310.0	174.5	177.0	202.5	235.5	262.0	282.0
MEAN		147.7	164.3	213.8	260.0	272.0	269.6	153.7	178.3	223.6	270.4	271.1	259.4
SD		52.1	49.1	61.8	61.7	70.6	79.9	54.7	62.0	66.1	68.9	74.2	87.6
Non-Diabetics Controls		Hyperthemia Condition						Control Condition					
AL		94.4	93.9	112.5	106.5	103.5	116.5	99.3	92.5	121.5	99.7	103.0	119.0
CJ		104.5	98.6	144.5	125.5	127.0	125.5	91.9	98.7	115.0	114.0	107.5	91.3
CR		84.2	84.2	104.5	80.3	72.3	69.7	80.1	80.1	98.6	64.7	111.0	66.8
DT		121.5	125.5	164.5	191.0	197.5	177.5	99.9	116.0	160.0	144.5	145.0	135.0
EG		95.9	95.4	126.0	132.5	139.5	122.0	92.5	88.6	119.0	146.5	116.5	112.0
MH		94.8	111.5	139.5	105.0	106.0	91.9	87.2	99.9	154.5	102.0	114.0	102.0
MR		90.8	100.2	147.5	82.1	77.5	75.3	84.9	118.0	136.5	90.4	64.5	66.8
MS		86.5	110.5	144.0	105.5	74.4	88.0	81.7	77.9	95.3	93.7	88.9	54.9
TS		107.5	130.0	176.5	209.0	160.0	165.0	103.5	120.0	171.5	203.0	186.0	150.0
MEAN		97.8	105.5	139.9	126.4	117.5	114.6	91.2	99.1	130.2	117.6	115.2	99.8
SD		11.7	15.1	23.0	45.3	42.7	37.8	8.4	16.0	27.1	41.2	34.3	32.7

Note. ID = identification, SD = standard deviation

Insulin Concentration (uU/mL) during a 75 g Oral Glucose Tolerance Test After Hyperthermia and Control Conditions

Type 2 Diabetics		Hyperthemia Condition						Control Condition					
ID	Time (min)	0	15	30	60	90	120	0	15	30	60	90	120
DA		6.5	6.4	8.4	10.8	10.9	11.6	5.8	9.0	10.4	10.4	9.6	10.0
EB		14.6	19.6	19.6	43.1	52.1	52.2	15.1	19.6	19.6	43.1	52.1	52.2
HD		20.3	21.8	43.7	34.2	34.7	36.7	31.1	41.7	43.0	49.9	38.3	57.9
JC		15.6	25.5	38.0	53.1	40.5	42.4	16.2	25.8	54.6	57.2	39.1	43.2
LA		8.1	14.2	11.3	17.6	23.3	24.9	11.9	14.8	17.7	25.9	24.4	36.4
MC		14.5	18.3	26.8	49.1	85.4	82.7	12.3	15.5	18.3	53.2	62.5	60.9
SH		21.1	24.8	25.0	28.4	33.0	33.9	17.0	19.5	21.6	25.0	28.5	35.3
SK		16.5	22.4	43.4	45.0	54.4	72.1	13.1	16.6	37.5	50.3	64.6	76.0
SM		26.3	40.6	40.9	54.9	57.7	52.4	26.9	36.0	44.7	55.3	46.8	50.0
MEAN		15.9	21.5	28.6	37.4	43.6	45.4	16.6	22.1	29.7	41.1	40.6	46.9
SD		6.2	9.3	13.6	15.7	21.8	22.3	7.8	10.6	15.4	16.6	18.0	18.8
Non-Diabetics Controls		Hyperthemia Condition						Control Condition					
AL		12.4	12.5	38.1	36.3	41.0	39.0	9.9	9.1	28.3	22.0	15.3	18.8
CJ		3.9	10.1	35.1	33.1	41.5	43.5	3.4	4.5	16.3	29.2	19.4	16.4
CR		7.9	16.1	41.5	15.9	24.0	17.4	13.2	17.5	51.0	25.1	34.3	29.4
DT		8.1	9.7	18.6	34.0	45.1	48.2	5.5	10.5	19.8	37.4	40.4	46.6
EG		5.3	12.2	27.1	33.7	32.1	30.7	4.3	11.1	31.2	39.8	37.0	25.5
MH		4.5	26.7	48.5	19.4	24.1	16.6	4.1	5.6	38.4	18.9	20.4	14.3
MR		8.6	24.3	61.1	40.0	32.1	31.2	6.6	12.2	93.6	121.5	55.5	57.3
MS		4.8	21.8	40.0	37.5	24.1	18.9	15.5	28.3	42.2	27.5	30.1	17.6
TS		5.1	11.7	19.0	31.2	31.4	38.1	4.8	11.2	21.9	40.0	47.1	46.9
MEAN		6.7	16.1	36.5	31.2	32.8	31.5	7.5	12.2	38.1	40.2	33.3	30.3
SD		2.7	6.5	13.7	8.2	8.1	11.7	4.4	7.1	23.7	31.4	13.4	16.0

Note. ID = identification, SD = standard deviation

C-peptide Concentration (uU/mL) during a 75 g Oral Glucose Tolerance Test After Hyperthermia and Control Conditions

Type 2 Diabetics		Hyperthemia Condition						Control Condition					
ID	Time (min)	0	15	30	60	90	120	0	15	30	60	90	120
DA		47.3	46.1	56.6	69.1	73.1	74.2	42.6	57.0	62.2	68.9	62.0	70.0
EB		56.2	56.2	66.1	104.6	131.2	152.0	56.0	56.0	90.6	111.4	126.7	128.9
HD		111.4	113.8	138.5	160.0	160.0	160.0	140.3	160.0	160.0	160.0	157.6	160.0
JC		73.4	81.8	105.2	148.3	134.1	153.5	61.4	71.5	107.9	151.1	126.6	136.7
LA		31.6	59.6	48.2	80.2	98.7	97.8	55.0	73.5	73.7	94.2	87.4	130.6
MC		60.8	55.1	74.6	115.0	178.8	153.2	44.7	47.4	60.4	121.6	119.7	139.7
SH		90.1	98.8	101.2	107.3	122.1	134.3	85.1	87.9	95.4	100.2	111.7	132.9
SK		83.7	93.9	120.7	139.4	131.9	176.5	68.9	79.1	113.1	142.7	151.9	192.2
SM		101.2	126.4	115.4	147.5	161.6	161.1	103.8	109.6	128.3	146.6	138.2	146.0
MEAN		72.9	81.3	91.8	119.0	132.4	140.3	73.1	82.4	99.1	121.9	120.2	137.4
SD		26.2	28.7	31.5	31.9	32.7	33.2	31.8	34.6	32.5	30.6	30.3	32.2
Non-Diabetics Controls		Hyperthemia Condition						Control Condition					
AL		55.3	48.0	91.8	106.4	106.7	118.9	48.7	47.0	83.2	84.1	61.1	74.8
CJ		28.4	45.0	100.7	91.7	121.3	139.7	23.7	61.1	99.2	107.5	93.3	81.9
CR		33.7	33.7	73.1	63.3	71.2	57.8	39.6	61.3	97.4	70.8	87.0	64.1
DT		55.8	58.6	80.0	125.4	146.8	167.9	44.5	50.7	84.5	139.6	132.7	150.5
EG		46.1	46.1	97.4	109.2	135.7	124.9	33.2	44.0	56.8	80.6	84.6	113.9
MH		32.2	74.0	120.3	107.2	105.5	94.6	25.4	29.7	88.4	85.8	79.4	77.8
MR		40.8	63.6	112.7	112.1	96.4	82.8	35.0	112.9	155.3	188.1	128.9	136.5
MS		30.2	66.3	115.1	136.1	102.8	83.4	91.8	84.8	123.9	125.6	112.2	109.1
TS		38.2	57.2	85.5	131.8	152.9	157.0	40.7	58.6	103.8	146.2	160.0	160.0
MEAN		40.1	54.7	97.4	109.2	115.5	114.1	42.5	61.1	99.2	114.3	104.4	107.6
SD		10.3	12.6	16.4	22.2	26.2	37.1	20.2	24.6	27.8	38.8	31.4	35.3

Note. ID = identification, SD = standard deviation

Leptin Concentration (pg/mL) during a 75 g Oral Glucose Tolerance Test After Hyperthermia and Control Conditions

Type 2 Diabetics		Hyperthemia Condition						Control Condition					
ID	Time (min)	0	15	30	60	90	120	0	15	30	60	90	120
DA		4256.0	3971.0	3936.5	4048.5	3728.5	3763.5	3797.5	3907.5	3877.0	4005.5	3560.5	3766.0
EB		19445.0	19445.0	20927.0	20903.0	18017.5	21870.0	18564.5	18564.5	19669.5	19433.0	19184.0	18261.0
HD		25889.0	25996.0	23973.5	25623.0	22589.5	22557.5	22613.5	22613.5	21242.5	21481.5	18185.5	19995.5
JC		22884.5	21516.0	21096.5	22526.0	18260.0	21080.5	14713.0	14387.5	13319.5	14486.5	13757.0	12348.5
LA		13373.5	20739.5	14400.0	19858.5	19478.5	19233.5	12305.0	14821.5	12836.5	14337.5	10235.5	14375.0
MC		29343.5	28308.5	30090.5	27838.5	28033.0	27673.5	27221.5	25174.5	24529.0	26100.5	21484.5	22690.5
SH		35281.0	36332.0	41212.5	36869.5	39382.0	42403.0	35427.0	34549.0	36424.5	37222.0	35468.0	35699.0
SK		34245.0	32633.5	32678.5	36351.5	25395.0	40061.5	28359.0	32581.0	37167.0	31327.5	27344.5	35417.5
SM		14058.5	15009.0	13767.0	15258.5	14079.0	15135.0	13953.5	14186.5	14307.5	13924.5	13586.0	13916.5
MEAN		22086.2	22661.2	22453.6	23253.0	20995.9	23753.1	19661.6	20087.3	20374.8	20257.6	18089.5	19607.7
SD		10337.8	9699.1	11205.2	10209.8	9837.0	11914.0	9709.0	9725.2	11032.2	10119.6	9435.5	10510.6
Non-Diabetics Controls		Hyperthemia Condition						Control Condition					
AL		35279.0	28276.0	25757.0	25161.0	22648.5	27540.5	19046.5	20579.0	19156.0	19445.5	18910.5	21184.5
CJ		2548.0	2055.5	1986.0	1859.0	2079.0	2151.5	3087.5	3518.5	3041.5	3088.5	2730.0	2941.5
CR		33549.0	33549.0	27482.0	36914.0	32224.0	32419.5	29270.0	29270.0	30475.5	29506.5	29411.0	29581.5
DT		11038.0	11142.5	10936.5	11146.5	11092.5	12662.5	11154.5	10650.5	10713.5	10822.5	10956.5	10533.0
EG		9515.0	9137.0	8086.5	9167.0	9176.5	10009.0	10044.0	7427.0	8314.5	8848.5	9447.0	9754.5
MH		3863.0	3822.5	3452.5	3656.5	3623.0	3686.0	3538.5	3309.5	2866.5	3230.0	2959.5	3385.5
MR		14683.0	16223.0	14073.5	15208.0	15305.5	15327.5	13196.0	12833.0	12500.5	13796.5	12248.5	12804.0
MS		7679.5	6959.5	7398.0	8109.0	7339.0	6372.0	14782.5	13496.5	12964.0	14656.0	12973.5	12781.5
TS		15806.0	15931.0	14969.5	16017.5	15613.5	15975.5	13041.5	12278.5	12764.0	12295.5	12667.5	13739.5
MEAN		14884.5	14121.8	12682.4	14137.6	13233.5	14016.0	13017.9	12595.8	12532.9	12854.4	12478.2	12967.3
SD		11907.9	10736.3	9005.8	11043.0	9564.3	10313.6	7940.5	8230.0	8446.0	8165.2	8105.3	8312.5

Note. ID = identification, SD = standard deviation

Incremental Area Under The Curve for Glucose, Insulin, C-peptide, and Leptin

Type 2 Diabetics	Glucose		Insulin		C-peptide		Leptin	
ID	Hyper	Control	Hyper	Control	Hyper	Control	Hyper	Control
DA	45555.0	45127.5	1161.7	1162.7	7699.2	7550.4	469818.8	457796.3
EB	20865.0	20502.8	4481.9	4485.8	12106.3	12374.7	2404035.0	2292690.0
HD	31233.8	33307.5	4080.1	5339.6	17657.1	18979.0	2908248.8	2476702.5
JC	25503.8	25455.0	4799.4	5273.4	14922.8	14342.2	2508832.5	1658381.3
LA	29981.3	37391.3	2129.8	2763.0	9049.9	10578.3	2204006.3	1556246.3
MC	23902.5	22402.5	6261.2	5119.6	14071.0	11738.5	3412987.5	2901588.8
SH	26396.3	27431.3	3444.1	3037.9	13328.8	12455.6	4660458.8	4319673.8
SKH	23028.8	21663.8	5500.4	5778.4	15540.4	15969.6	3934923.8	3829087.5
SMH	29591.3	27675.0	5890.7	5562.0	16942.1	16045.5	1747481.3	1673430.0
MEAN	28450.8	28995.2	4194.4	4280.3	13479.7	13337.1	2694532.5	2351732.9
SD	7284.2	8180.8	1708.0	1593.2	3373.9	3399.7	1233442.1	1200907.9
Non-Diabetics Controls	Hyper	Control	Hyper	Control	Hyper	Control	Hyper	Control
ALH	12694.9	12729.4	4040.4	2249.1	11374.5	8419.4	3115657.5	2350991.3
CJH	14971.5	12771.0	3863.7	2162.1	11641.6	10578.1	245040.0	363045.0
CRH	9867.8	10291.1	2691.7	3731.0	7304.8	9103.8	3933630.0	3555521.3
DTH	20812.5	16799.3	3720.6	3678.0	13786.0	13421.5	1353101.3	1295835.0
EGH	14975.3	14269.9	3268.4	3588.1	12448.3	8849.8	1090803.8	1068993.8
MHH	13230.8	13638.8	3081.1	2374.2	11858.4	8748.4	437666.3	377145.0
MRH	11419.9	11125.1	4432.7	9220.0	11292.8	17007.2	1815438.8	1546136.3
MSH	12260.6	10225.5	3394.1	3484.3	12229.7	13520.8	887463.8	1625613.8
TSH	20272.5	20355.0	3091.8	4013.2	13961.6	15106.1	1882886.3	1524161.3
MEAN	14500.6	13578.3	3509.4	3833.3	11766.4	11639.5	1640187.5	1523049.2
SD	3782.3	3282.9	548.0	2141.8	1932.8	3194.0	1218084.2	983868.8

Note. ID = identification, SD = standard deviation