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The effects of type 2 diabetes on body heat storage during and following exercise

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Abstract

Background: Elevated mortality rates and impaired local heat loss mechanisms have been found in Type 2 diabetes mellitus (T2DM) during heat stress. However, little is known about the effects of T2DM on whole body heat loss.

Objective: To compare body heat content (H_b) between T2DM and a matched control group (CON) during and after exercise in the heat.

Methods: Fourteen participants (7 T2DM; 7 CON) cycled in a calorimeter for 1 hour, and recovered for 1 hour on two separate occasions (24 and 30°C).

Results: The T2DM group had similar sweating responses ($p>0.09$) but reduced maximum skin blood flow (SkBF) vs. CON, ($p=0.045$, 24°C; $p=0.049$, 30°C). The change in H_b was not different between groups during exercise or recovery ($p>0.09$).

Conclusion: These results suggest that impaired sweating and SkBF in T2DM may be limited to certain areas of the body and do not interfere with whole body heat loss.

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Abbreviations

T2DM – type 2 diabetes mellitus

CON – control group

DARE – Diabetes Aerobic, and Resistance Exercise study

H_b - body heat content (expressed in kJ)

H_E – evaporative heat loss (expressed in kJ/period of time or kJ/min)

H_D – dry heat loss (expressed in kJ/period of time or kJ/min)

SkBF – skin blood flow (expressed in arbitrary perfusion units)

Max SkBF – maximum skin blood flow

FFM – fat free mass: includes muscle, tissue, organs, and bones

BSA – body surface area (m^2)

LSR – local sweat rate (g/cm^2)

HR – heart rate (bpm)

SBP/DBP – systolic/diastolic blood pressure (mmHg)

MAP – mean arterial pressure (mmHg)

CVC – cutaneous vascular conductance: calculated as SkBF/MAP

T_{re} – rectal temperature (°C)

T_{core} – core temperature (°C)

T_{sk}– skin temperature (°C)

PE – perceived exertion (Borg Scale, 6-20)

Hb_{A1c} - Glycated hemoglobin, (%)

Definitions

%CVC – cutaneous vascular conductance represented as a percentage of maximal skin perfusion

Glycated hemoglobin - (% of total): hemoglobin that has been exposed to glucose – provides an idea of the average amount of glucose passing through the blood over the last 14-120 days (Dean, 2008).

VO_{2max} - a measure of functional capacity characterized by the body's ability to oxidize metabolic substrates or use oxygen (Rowell, 1974) and is determined by graded exercise testing

Sudomotor rhythm – the pulsatile tendency by which sweat-gland output is influenced; sweat is excreted in different amounts and at different times based on the frequency and number of neural signals acting on the sweat gland by the sympathetic nervous system – there is often a large secretion followed by a small secretion, and this pattern repeats over time, especially during exercise or heat stress (Sugenoya & Ogawa, 1985).

Temperature -an arbitrary scale (typically based on how mercury responds to gains in kinetic energy, i.e. heat gain = increase in volume and pressure within a thermometer) that is used to measure the amount of heat energy that is transferred from one object to another when a measuring instrument is inserted between two objects.

CHAPTER I

Introduction

The frequency of extreme heat events has increased in the past decade and has been identified as a major health risk by organizations such as the World Health Organization and the International Panel of Climate Change (Bernstein *et al.*, 2007; Costello *et al.*, 2009; Luber & McGeehin, 2008; Patz *et al.*, 2005). Current research shows that those who are at the greatest risk for illness, injury and death during extreme weather are older adults (Luber & McGeehin, 2008), obese individuals (Chung & Pin, 1996), and those with chronic disease (Rey *et al.*, 2007; Semenza *et al.*, 1999). It has been projected that the number of older adults will increase exponentially in the next few decades, paralleled by increases in obesity and chronic diseases such as type 2 diabetes mellitus (T2DM) (Ford & Mokdad, 2008; Lee *et al.*, 2009; Raine, 2004). The combination of these future predictions in population health and climate change has created an urgent need for further study of heat stress in older individuals with T2DM. Specifically, investigation needs to be carried out to discern the degree of impairment in thermoregulatory capacity, if any, in response to exercise and heat exposure.

When humans are exposed to ambient conditions which are hotter and/or more humid than the individual is accustomed to, there are substantial physiological challenges imposed on the body (Kenney, 1996; Rowell, 1974). During physical work or exercise in these conditions, the body is required to make further physiological adjustments in order to dissipate heat and maintain core temperature (Nielsen *et al.*, 1984; Rowell, 1974). The primary method of heat dissipation in these situations is the evaporation of sweat from the skin (Nadel *et al.*, 1971b; Saltin *et al.*, 1970). Therefore, the evaporation of sweat

becomes more crucial than conductive, or radiative heat exchange during exercise in hot or humid environments, and is often responsible for 60-80% of total heat loss (Kenney & Zeman, 2002; Nadel et al., 1971b). After exercise however, there is a drastic drop in evaporative heat loss, despite elevated levels of heat within the body (W. S. Journeay *et al.*, 2004; Shibasaki *et al.*, 2004). In order to rid the body of this excess heat stored during exercise, dry heat loss (conduction/radiation/convection) makes a greater contribution to total heat loss by increasing skin perfusion or skin blood flow (SkBF)- which allows core temperature to begin its decent to pre-exercise levels (W. S. Journeay et al., 2004; Rowell *et al.*, 1966; Thoden *et al.*, 1994).

In healthy individuals who are exposed to environmental heat stress, these cooling mechanisms effectively facilitate heat loss; however, when sweating and SkBF are attenuated, there may be an increased risk for heat illness and injury. Findings of decreased sweating and SkBF during global and local heating in older individuals with T2DM (Ohtsuka *et al.*, 1995; Petrofsky *et al.*, 2005a; Stansberry *et al.*, 1997) have led researchers to suggest that whole body heat loss may be impaired during heat stress situations, which may explain the increased prevalence of heat-related morbidity and mortality in the older T2DM population. It is not known, however, if these changes in local heat loss mechanisms are sufficient to interfere with changes in whole body heat storage during and after exercise in a hot environment.

As mentioned, older adults, people who are obese, those who have cardiovascular disease, and those with T2DM are at the greatest risk for heat-related illnesses or injuries (G. Kenny, Yardly, J., Brown, C., Sigal, R.J., Jay, O., 2009). If diabetes is poorly managed for an extended period of time, there can be deleterious effects on physiological functions (Cersosimo & DeFronzo, 2006; B. A. Perkins *et al.*, 2001; Shun *et al.*, 2004).

Combined with the changes that occur due to aging, older adults with poorly managed T2DM can experience impairments in thermoregulatory capacity (Charkoudian, 2003; Holowatz *et al.*, 2007; Kenney & Hodgson, 1987; Ohtsuka et al., 1995). Cardiovascular disease, hypertension, neuropathy, retinopathy, obesity, and hyperlipidemia are just some of the complications that accompany T2DM (Finegood, 2004; Mo *et al.*, 2006; I. Perkins, 2004; A. I. Vinik *et al.*, 1992). However, the degree of influence that these co-morbidities have on people with T2DM -in terms of their ability to dissipate heat from a whole body perspective, is unclear.

Various studies suggest that T2DM is often accompanied by a range of physiological impairments, the majority of which are exacerbated when diabetes is poorly controlled over a long period of time (Cersosimo & DeFronzo, 2006; B. A. Perkins et al., 2001; A. I. Vinik *et al.*, 2000). These impairments include: endothelial dysfunction (Cersosimo & DeFronzo, 2006; Stansberry *et al.*, 1999), reductions in skin sensitivity to hot and cold (Aprile, 2004; Ijff *et al.*, 1991), reduced or altered skin blood flow (Levy *et al.*, 1989; Petrofsky et al., 2005a; Wick *et al.*, 2006), and reduced sweating (Petrofsky et al., 2005a). Complications of T2DM have also been purported to cause a decreased ability to: excrete sweat, actively vasodilate blood vessels (Wick et al., 2006), and transmit nerve impulses to the skin and blood vessels (Levy et al., 1989; A. I. Vinik *et al.*, 2001) which can impair heat dissipation. This reduced potential for evaporative heat loss -especially during extreme heat stress situations- increases the risk for heat illness and injury in individuals with T2DM who have developed these impairments.

In individuals who have T2DM, co-morbidities such as hypertension and neuropathy, can further increase susceptibility to heat illness and injury (Chung & Pin, 1996; Kenney, 1985; Sun *et al.*, 2008). In order to prevent vulnerable individuals from

succumbing to heat illness and injury, it is necessary to understand and separately investigate risk factors such as age, obesity, nerve damage, and T2DM. This task is complicated because many vulnerable individuals have more than one of these risk factors. For example, the majority of individuals with T2DM are obese, over the age of 60, or both (Public Health Agency of Canada, 2008). As one ages, fitness and the ability to regulate body temperature deteriorates (Ho *et al.*, 1997; Inoue *et al.*, 1999; Inoue *et al.*, 2004; Kenney & Hodgson, 1987). Evidence also suggests that individuals who are obese exhibit reduced heat and exercise tolerance (Chung & Pin, 1996). When an individual suffers from more than one of these complications, the body's ability to maintain thermal equilibrium may be severely compromised; however, there is no evidence to confirm the additive effects of physiological impairments when exposed to exercise and hot environments.

Though numerous studies suggest that thermoregulation is impaired in individuals with T2DM due to alterations of sweating and skin blood flow during heat stress, very few studies have actually confirmed this by measuring the changes in whole body heat storage or core temperature. Furthermore, epidemiological studies of heat-wave related morbidity and mortality did not provide direct evidence of physiological impairments in heat loss mechanisms due to the nature of the information available for analysis, leaving a gap in the literature regarding thermoregulation in vulnerable individuals during heat stress (G. Kenny, Yardly, J., Brown, C., Sigal, R.J., Jay, O., 2009). The specific physiological and environmental factors that contribute to impaired thermoregulation must be clarified from a whole body perspective. The following study was implemented to develop a better understanding of the effects of T2DM on local and whole body heat loss and changes in body heat content (ΔH_b) while performing physical activity in hot

ambient conditions.

1.1 Rationale

Research has shown that, at rest and during heat exposure, local skin blood flow and sweating responses can be attenuated in older individuals with T2DM compared to non-diabetic controls (McLellan *et al.*, 2009; Petrofsky et al., 2005a; Wick et al., 2006). These impairments are suspected to be a result of various pathological defects such as nerve damage, endothelial dysfunction, and impaired sudomotor activity. Because both autonomic and local nerve control and responsiveness of blood vessels in the skin are essential to facilitate changes in SkBF and sweating (Kellogg, 2006; Minson *et al.*, 2001; Shibasaki *et al.*, 2006a; Sugenoya *et al.*, 1990), alterations to these mechanisms may impair the individual's ability to effectively transfer heat between the body and the environment .

Of particular interest to this study, is the knowledge that evaporative heat loss is largely controlled by SkBF and sweating (Brooks, 1996). Both local and whole body sweating are well known to play a crucial role in modulating whole body heat loss during and after exercise, as well as during heat stress (Kondo *et al.*, 2001; Nadel et al., 1971b; Saltin *et al.*, 1972; Shibasaki *et al.*, 2006b), whereas the direct influence of changes in local SkBF have not been examined in terms of the effects on whole body heat loss. -It is important to note here, that SkBF and sweating do not work independently of one another, but the two mechanisms can overlap (and sometimes work simultaneously) which can greatly affect the body's capacity for heat loss in response to exercise and heat exposure. - Indeed, only small alterations in SkBF and sweating are necessary for evaporative heat loss to occur; so if SkBF and/or sweating are impaired in any way, it

stands to reason that both evaporative and whole body heat loss may also be impaired. Researchers have often assumed that a reduction in SkBF and sweating, which sometimes occurs in T2DM and with aging, would lead to a reduction in the body's ability to effectively dissipate heat through evaporative heat loss, however, such a finding has yet to be confirmed directly. Instead, the majority of current research on heat loss and diabetes only includes findings of local heat loss mechanisms in response to heat stress, such as reduced or delayed vasodilation of local blood vessels, reduced quantities of sweat, and decreased sudomotor rhythm at certain sites on the body/skin (Petrofsky et al., 2005a; Sun et al., 2008; Wick et al., 2006). However, none of these reductions have been expressed in terms of their effects on body heat content (H_b) for the individual as a whole.

Quantification of H_b requires measurement of the rates of whole body heat loss and heat gain, while core and skin temperature, local sweat rate, and SkBF measurements can provide indicators of how heat is transferred (Reardon *et al.*, 2006; Snellen, 2000; Vallerand *et al.*, 1992). Environmental physiology studies use direct calorimetry to take simultaneous minute-by-minute measurements of the individual heat balance components to estimate the rate of heat storage as well as ΔH_b (G. P. Kenny *et al.*, 2009; G. P. Kenny *et al.*, 2008b). This process requires that the rate of metabolic heat production be estimated by respiratory gas analysis under constant ambient conditions, while the rate of net heat loss from the body is determined from the direct measurement of the rates of sensible (radiation, conduction/convection) and insensible (evaporation/convection from sweating and respiration) heat loss using a direct calorimeter (Reardon et al., 2006; Snellen, 2000). Combined with local measurements, direct calorimetry can be used to examine the interactions between local and whole body changes in heat exchange during exercise in the heat (Snellen, 2000).

This study is one of the first to quantify the changes in the rate of H_b while measuring changes in SkBF and sweating in individuals with T2DM during and after moderate-intensity aerobic exercise in a hot environment using direct calorimetry. Findings will help identify the risks associated with performing physical activity in the heat and may aid in the creation of practical safety guidelines for individuals with T2DM who work or exercise under similar conditions.

1.2 Purpose

The following study was conducted to evaluate the changes in body heat content and whole body heat loss in individuals with type 2 diabetes during and following exercise performed in temperate (24°C) and hot (30°C) ambient conditions.

1.3 Hypothesis

We hypothesized that individuals with T2DM would demonstrate an attenuation in the rate of whole body heat loss during exercise and recovery in the hot condition and would subsequently have higher net body heat content by the end of these experimental sessions as compared to the CON group.

CHAPTER II

Literature Review

2.0 Human Thermoregulation: An overview

Humans are homeothermic, meaning that core body temperature is maintained despite changes in metabolic heat production or changes in the environment (Brooks, 1996; Webb, 1995). Thermal balance, and therefore a stable core temperature, is dependent on the rate and direction of heat exchange between body tissues and the environment (Hammel *et al.*, 1963; Nishi & Gagge, 1971). Core temperature reflects the balance between thermolysis (heat loss processes) and thermogenesis (heat generating processes) within the body and is measured by thermometry (Hammel et al., 1963; Nishi & Gagge, 1971; Rowell, 1974). At rest, the human body constantly produces heat which is dissipated to the environment (Webb, 1995). If the heat generated from the body cannot be dissipated, the accumulation of heat within the body can lead to serious heat illness or even death (Bates *et al.*, 1996; Rowell, 1974; Webb, 1995). When core temperature fluctuates, the healthy human body compensates for these changes by altering metabolism, behavior, or heat loss mechanisms. These changes facilitate heat exchange by conduction, radiation and evaporation (Brooks, 1996; Rowell, 1974; Webb, 1995). In order for core temperature to be maintained, the difference between the rates of net heat production and net heat loss must be zero. As mentioned, the most feasible way to determine heat loss and heat gain in humans is to estimate the changes in body heat content (ΔH_b) by whole body calorimetry (Snellen, 2000; Vallerand et al., 1992). This measurement system is described in a review by Reardon et. al (Reardon et al., 2006). In summary, the process requires simultaneous minute-by-minute measurements of the individual heat balance components; heat produced and heat lost (Reardon et al.,

2006; Snellen, 2000). The rate of metabolic heat production is measured by respiratory gas analysis, -indirect calorimetry- while the rate of whole body heat loss is determined by measuring sensible and insensible heat loss (Reardon et al., 2006).

The transfer of body heat energy by conduction, radiation, evaporation, and convection is dependant on temperature gradients within the body and between the body and the environment (A. P. a. N. Gagge, Y., 1977; Johnson *et al.*, 1996; Nishi & Gagge, 1971; Webb, 1995). More specifically, conduction is dependant on the temperature gradient between two surfaces that are in direct contact with one another (i.e. skin and blood) whereas radiation does not require direct contact to transfer heat energy; instead, electromagnetic waves transfer heat between an object and its surroundings (i.e. sun and skin) (A. P. a. N. Gagge, Y., 1977; Nishi & Gagge, 1971). Evaporation of heat from the body is primarily accomplished through the vaporization of sweat and is primarily dependant on the gradient of partial pressure of water (P_{H2O}) between the skin and the air (also known as ambient humidity); however, evaporation also occurs accross the gradient between the air and the pulmonary surface in the lungs (Brooks, 1996; Nishi & Gagge, 1971; Webb, 1995). The speed with which water evaporates is also influenced by air temperature and air flow over the surface in question. Convection, however, is dependant on the rate of flow of a gas or liquid over a contact surface (A. P. a. N. Gagge, Y., 1977) and affects the rate of heat exchange by interacting with conduction and evaporation, the both of which can be enhanced by an increase in fluid flow over the skin (Webb, 1995). The interaction of man with the environment is conceptually demonstrated using the human heat balance equation (A. P. a. N. Gagge, Y., 1977; Nishi & Gagge, 1971):

$$M - W = (K + C + R + E_{SK}) + (C_{RES} + K_{RES} + E_{RES}) + S \quad \text{.....(1)}$$

Where:
M = rate of metabolic heat production
W = rate of mechanical work (effectively = 0)
K = rate of conductive heat loss
C = rate of convective heat loss from the skin
R = rate of radiative heat loss from the skin
E_{SK} = rate of evaporative heat loss from the skin
C_{RES} = rate of convective heat loss from respiration
K_{RES} = rate of conductive heat loss from respiration
E_{RES} = rate of evaporative heat loss from respiration
S = rate of body heat storage (all units $W \cdot m^{-2}$)

2.0.1 Models of human thermoregulatory control

Different theories exist to explain body core temperature regulation, namely 'set-point theory', 'the inter-threshold zone', and 'reciprocal inhibition'. Set point theory suggests that the body has a specific internal reference temperature which it strives to maintain under all circumstances (Boulant, 2006; Hammel et al., 1963) so that the body can function optimally, using the least amount of resources. Hammel (1963) proposed that any deviations from this central reference temperature or 'set-point' result in an error signal which activates the appropriate thermo-effector mechanisms aimed at re-establishing thermal homeostasis (Hammel et al., 1963). This thermoregulatory system operates in a negative feedback loop between the body and the hypothalamus (Hammel et al., 1963; Mack, 2004) such that when T_{core} increases thermosensitive neurons –primarily in the preoptic anterior hypothalamus- create a reaction which activates heat loss mechanisms such as SkBF and sweating (Hammel et al., 1963; Wyss *et al.*, 1974).

Alternatively, some research studies suggest that T_{core} is regulated within a thermo-effector threshold zone instead of just one set temperature point (Gisolfi, 1984; Mekjavic & Eiken, 2006; Sessler, 2009). This theory suggests that adjustments in heat

loss (sweating), and heat gain (shivering), have a thermo-effector threshold zone which must be reached before heat loss or heat generation begins (Mekjavic & Eiken, 2006; Sessler, 2009). The idea of the 'threshold zone' means that there is a margin of variation around a set point temperature for which the body can still maintain optimal bodily functions before heat loss or heat gain mechanisms become activated.

The idea of reciprocal inhibition suggests that heat loss and heat production mechanisms work simultaneously (almost in opposition to one another) to maintain thermal homeostasis, as opposed to set-point theory, which states that heat loss and heat producing mechanisms take turns independently of one another (Hammel et al., 1963; Mekjavic & Eiken, 2006).

As more studies are published to support and refute certain aspects of these theories, the scientific community is forced to take all information into consideration when investigating the topic of human body core temperature regulation. Though often left out of thermoregulation theories, non-thermal influences play a role in heat gain and heat loss, and therefore must also be considered when attempting to understand the regulation of T_{core} (Mekjavic & Eiken, 2006) By acknowledging the strengths and weaknesses of each theory, a more complete explanation of human thermoregulation can be provided.

2.0.2 Thermoregulatory adaptations to heat stress

The human body is able to dissipate heat at rest, during exercise, and during recovery by making a series of adjustments to physiological functions such as blood flow and sweating (Carter *et al.*, 2002; Kellogg *et al.*, 1993; Stolwijk *et al.*, 1968; Webb, 1995; Wyss et al., 1974). At rest in hot ambient temperatures (> 30°C or > skin temperature),

the human body gains heat from the environment via radiation and conduction. When the hypothalamus senses that the body is storing more heat than normal, sweating and/or SkBF are activated as a means to dissipate heat to the environment via conduction/convection, radiation and evaporation (Blatteis *et al.*, 1996; A. P. a. N. Gagge, Y., 1977; Kondo et al., 2001). Skin blood flow, which is directly influenced by changes in vasomotor tone, serves as one of the main avenues through which heat can be transferred at rest (Johnson, 1986; Kellogg *et al.*, 1990; Pergola *et al.*, 1994; Wyss et al., 1974). Vasomotor tone (which is a balance of vasoconstrictor and vasodilator influences on blood vessels) is the primary mechanism by which T_{core} is maintained at a steady state during most daily activities and across small variations in ambient temperature (Pergola et al., 1994; Rowell, 1984). Consequently, even the smallest changes in blood flow can cause relatively large amounts of heat loss, (Charkoudian, 2003; Rawson & Randall, 1961; Rowell, 1983).

Skin blood flow and sweating, each have a threshold which must be reached before heat loss begins to occur (Nadel & Stolwijk, 1973b; Rawson & Randall, 1961). When the body generates or absorbs enough heat energy to go beyond the upper limits of the thermo-effector threshold, SkBF is increased and sweating is induced to offset the excess heat (Mekjavic & Eiken, 2006; Sessler, 2009). This increase in SkBF creates a temperature gradient between the skin and the air so that heat can be dissipated from the body to the environment – but this can only occur when ambient temperatures are lower than skin temperatures (A. P. a. N. Gagge, Y., 1977). When SkBF is increased, it facilitates conductive, convective, and evaporative heat loss and is primarily mediated by activation of sympathetic vasodilator nerves in the skin (Kellogg, 2006; Kellogg *et al.*, 1995; Mekjavic & Eiken, 2006; Pergola et al., 1994).

Skin blood flow can also be increased due to endogenous heating of the skin, which is regulated by local reflex mechanisms instead of the central nervous system (Charkoudian, 2003; Rowell, 1984; Wyss et al., 1974). Local responses involve sensory nerve mechanisms at the skin level that react rapidly to C-fiber afferents which cause localized vasodilation and sensation of heat through a complicated series of reactions (DiPasquale *et al.*, 2003; Kellogg et al., 1995). Central control of SkBF by the hypothalamus, however, is activated when T_{core} is elevated, and is responsible for active vasodilation which greatly increases skin perfusion (Blatteis et al., 1996; Nielsen et al., 1984; Rowell, 1983). It must also be noted that local and central control mechanisms can overlap (Pergola *et al.*, 1996). Active cutaneous vasodilation, which is primarily mediated by central control through the sympathetic nervous system, is susceptible to changes in local skin temperature (Kellogg *et al.*, 1989). Reports indicate that active vasodilation is dependent on both the sensitivity of local cells to nitric oxide and the availability of endothelial-derived nitric oxide (Houghton *et al.*, 2006; McCord *et al.*, 2006; Minson et al., 2001). Nitric oxide is required to activate sweat glands in the skin, and to relax smooth muscles cells of the blood vessels enabling vasodilation, so if there is not enough nitric oxide or if there is a reduced sensitivity, sweating and SkBF can become impaired (Holowatz *et al.*, 2003; Houghton et al., 2006; Kellogg, 2006; McCarty *et al.*, 2009).

Both non-thermal and thermal influences can cause the human body to sweat through either eccrine or apocrine sweat glands (Kondo et al., 2001; Shibasaki et al., 2006b; Wollina *et al.*, 2007). The apocrine sweat glands are located primarily on the palms of the hands and soles of the feet, and other non-hairy parts of the body (Wilke *et al.*, 2007). Fluid secretion from these glands is most apparent when a person is nervous or if they have eaten spicy food. Sweat that is secreted from the apocrine glands is

primarily triggered by the gustatory response whereas the eccrine glands are primarily influenced by body and skin temperatures (Kondo et al., 2001; Shibasaki et al., 2006b). The eccrine sweat glands are distributed over the majority of the body's surface and are generally recruited to facilitate heat loss when the body's core temperature increases due to elevated ambient conditions or exercise (DiPasquale et al., 2003).

At rest, both sweating and SkBF can occur before any change in core temperature, and without meeting the threshold for sweating or active vasodilation (drastic increase in SkBF), indicating that peripheral receptors are in control (DiPasquale et al., 2003; Nadel & Stolwijk, 1973a; Shibasaki et al., 2006b; Vanbeaumont & Bullard, 1965; Wyss et al., 1974). Sweating during exercise or extreme heat stress, however, is primarily controlled centrally by the preoptic hypothalamus (Rowell, 1974; Saltin et al., 1972; Stolwijk et al., 1968). In order to initiate the sweating process, the preoptic hypothalamus sends and receives neural signals to the junction of peripheral nerves in the sweat gland and the clustering of sympathetic nerve terminals around the secretory coil of the sweat gland (Shibasaki et al., 2006b). Researchers have measured skin sympathetic nerve activity (SSNA) to quantify the amount of influence that neural signals have over the control of sweating (Shibasaki et al., 2006b; Vissing *et al.*, 1991). Using this method, it was noted that during heat stress, SSNA was partially synchronized with pulsatile sweat expulsion, indicating that central mechanisms play a significant role in the sweating process (Sugenoya *et al.*, 1995). Pulsatile sweat expulsion is also known as sudomotor rhythm, and is controlled by the sympathetic nervous system (Sugenoya & Ogawa, 1985). Sugenoya (1998) suggests that sweating is controlled by sudomotor mechanisms, which are approximately 80% synchronized with SSNA (Sugenoya *et al.*, 1998). However, the influence of SSNA on sweating can be reduced due to local influences which heat or cool

the skin and consequently heat and cool the sweat glands (Vanbeaumont & Bullard, 1965). For example, local temperature of the sweat gland (as indicated by skin temperature) can be a limiting factor in the process of heat exchange between the body and its environment, especially if the air temperature is hotter than the skin (Nadel *et al.*, 1971a; Nadel *et al.*, 1973). On the other hand, local heating has been shown to accentuate the sweat rate by enhancing the release of neurotransmitters such as acetylcholine, or increasing the sensitivity of receptors on the sweat gland itself (DiPasquale et al., 2003; Kondo et al., 2001). Kondo (Kondo et al., 2001) and Randall (Randall, 1946) suggest that during heat stress, an increase in evaporative heat loss is mediated by increases in sweat production primarily through adjustments in the number of sweat glands followed by a change in the amount of sweat released per gland. From this understanding of chemical and neural coordination, it can be extended that control of sweating as a means of heat exchange at rest is influenced by both internal and external heat sources, while being controlled through the activity of both peripheral and central mechanisms (Nadel et al., 1971b; Shibasaki et al., 2006b; Wyss et al., 1974).

Alterations of these mechanisms can enhance the rate at which heat is exchanged between the core of the body, the skin, blood, and the environment. Factors such as aerobic fitness, body fat, heat acclimation, and hydration status have all been shown to influence SkBF, sweating and T_{core} response during exercise and/or heat exposure (Budd, 1991; Havenith & Middendorp, 1990; Ho et al., 1997; McLellan et al., 2009; Nadel *et al.*, 1980; Nielsen et al., 1984; Rowell, 1974; Shibasaki et al., 2006b). Increased fitness or heat acclimation, for example, can provide an individual with physiological adaptations which are advantageous in maintaining core temperature despite high or prolonged heat stress (Gonzalez *et al.*, 1974; Inoue et al., 1999). Studies have shown that elevated

aerobic fitness and heat acclimation can cause a shift in the thresholds for cutaneous active vasodilation and sweating, which enable these heat loss mechanisms to begin at a lower core temperature relative to individuals with lower aerobic fitness or who are not heat-acclimated (Armstrong *et al.*, 2005; Inoue et al., 1999; Johnson, 1998). These adaptations may enable more efficient heat loss compared to individuals with lower aerobic fitness, however, since it is unclear if there are any changes in the way heat is gained due to elevated aerobic capacity, the effects on net body heat storage are unknown.

2.0.3 Exercise in the heat

Of particular interest in this study, are the thermoregulatory adaptations made by the cardiovascular system during exercise in the heat. Changes in SkBF and metabolism must occur during exercise in a hot environment in order to maintain core body temperature and sustain muscular activity (A. P. a. N. Gagge, Y., 1977). In healthy individuals, the demands to cool the body during exercise in the heat are met by increasing skin perfusion and sweating (Blatteis et al., 1996; Webb, 1995). Blood is redistributed from areas of the body which do not require as much blood flow as working muscles and skin, such as the kidneys and spleen. When exercise is performed in cool, dry, ambient conditions, most of the heat at the skin surface is dissipated by conduction because the temperature gradient between the skin and the air will favour heat transfer from the skin the surrounding environment (Blatteis et al., 1996; Kenney & Zeman, 2002; Pergola et al., 1996) –note, however, that this is highly dependent on skin perfusion-. If air current over the skin surface increases, heat loss by conduction will be favoured by convection. The main avenue of heat loss during exercise in the heat, however, is by

evaporation at the skin surface (Hammel et al., 1963; Saltin et al., 1970). In order for sweat to evaporate, the skin must be heated to temperatures that are warmer than the surrounding air temperature; this is accomplished by increased skin perfusion. However, since evaporation is dependant on the partial pressure gradient of water, relative ambient humidity must not exceed ~80% or sweat will not evaporate off of the skin. Evaporation of sweat will cool skin temperature, which cools the blood at the skin surface so that warm blood is cooled and does not return to the core allowing the body to effectively dissipate heat (Boulant, 2006). During exercise in the heat, the rate of sweat production increases significantly, especially once the hypothalamus senses that there is a substantial rise in mean body temperature (Nadel, 1980); this is accomplished by temperature sensitive neurons which identify changes in blood temperature in the hypothalamus (Charkoudian, 2003; Johnson, 1992; Nadel et al., 1971a).

2.0.4 Regulation of core temperature during exercise

During exercise, convective heat transfer must be dramatically increased because there is an increased production of metabolic heat due to the sustained contraction of the active musculature (Kenney, 1998). In order to offset an increase in core temperature and re-establish thermal balance, the rate of heat loss must be increased. However, at the start of exercise, there is delay in the redistribution of blood to the skin due to strong vasoconstrictor drive; this inhibits heat loss at the skin because blood is rushed to the muscle to provide the necessary nutrients and oxygen needed to sustain muscular contractions (Nielsen et al., 1984). This delay results in a mismatch between the rate of heat production and heat loss such that there is rapid increase in body heat storage and therefore core temperature (Nielsen et al., 1984). As core temperature increases, skin

perfusion is enhanced by active vasodilation and heat loss can occur simultaneously with sustained muscular activity. The excess heat produced during exercise needs to be balanced by a similar amount of heat loss. To meet this demand, there is an increase in SkBF and active cutaneous vasodilation (W. Journeay *et al.*, 2005; W. S. Journeay et al., 2004; G. P. Kenny *et al.*, 1997a). When exercising in a hot environment, there is an even greater need to increase SkBF and sweating due to the increased heat stress on the body (DuBois & DuBois, 1916). Under these circumstances, there is a competition between vasoconstrictor and vasodilator influences for control of blood flow throughout the body (Charkoudian, 2003; Kellogg *et al.*, 1991; Nielsen et al., 1984; Rowell, 1974). On one hand, the metabolic rate of muscles is increasing, causing a heightened demand for blood flow to that area to sustain activity (Charkoudian, 2003; Nadel *et al.*, 1979). In response to this demand from the active muscles, local metabolites and neural signals from the central nervous system combine to increase vasodilation and facilitate continued activity (Hammel et al., 1963; Kellogg et al., 1991; Nadel *et al.*, 1977). On the other hand, the heat being generated by exercise is being stored within the body (as evidenced by increased T_{core}) and is offset by heat loss through the skin (Nielsen et al., 1984; Webb, 1995). This creates a competition for blood flow between the skin, and the active muscles (Charkoudian, 2003; Kenney & Johnson, 1992). To maintain homeostasis during exercise, and/or heat exposure, the human body undergoes multiple, integrated changes to the physiological control systems (Nadel et al., 1977; Rowell, 1974; Sessler, 2009; Webb, 1995). Blood is shunted away from non-essential organs, cardiac output is increased, body tissue temperature changes to facilitate gas, nutrient, and waste exchange, while hormones, -like insulin and epinephrine- are released to facilitate glucose uptake and contribute to the active vasodilation of blood vessels in the skin (Brooks, 1996;

Charkoudian, 2003; Derouich & Boutayeb, 2002; Rowell, 1974; Rowell *et al.*, 1968).

2.0.5 Regulation of core temperature after exercise

One of the most prominent factors influencing the distribution of blood flow during recovery from dynamic exercise is the need to maintain blood pressure while simultaneously maintaining heat loss capabilities in order to reduce the elevated T_{core} (W. Journeay et al., 2005; G. P. Kenny *et al.*, 1997b; Pivarnik & Wilkerson, 1988). During inactive recovery, the need for blood flow to the muscles decreases due to lack of demand (W. Journeay et al., 2005). At this stage, the muscles no longer require high blood flow (like during exercise), but the systemic blood vessels and arteries require blood to maintain blood pressure; yet the skin also needs to sustain its elevated blood flow to dissipate the residual heat created during exercise (W. S. Journeay *et al.*, 2006; Thoden et al., 1994). Shunting of blood occurs again, as during exercise, however in recovery, blood volume is redistributed to maintain SkBF and blood pressure at the same time in healthy individuals (W. S. Journeay et al., 2004; Pivarnik & Wilkerson, 1988). During inactive recovery (up-right seated/standing), blood vessels in the lower legs often undergo venous blood pooling due to withdrawal of the muscle pump (Carter et al., 2002; Thoden et al., 1994). In this situation, blood pressure also drops, which is reflected by a decrease in mean arterial pressure (MAP) (W. S. Journeay et al., 2004; Kellogg et al., 1990; G. P. Kenny *et al.*, 2008a). This causes blood to remain in the arteries of the body, leaving a limited supply of blood to be sent to the skin to maintain thermal balance (Fisher, 1999). Research has shown that sweating can be maintained – to a lesser degree than during exercise- during recovery from exercise if an active or passive protocol is followed (Carter et al., 2002; Wilson, 2004).

When the demand for heat loss is decreased, which occurs during recovery from exercise, sweating continues to happen, however the amount and the rate at which sweat is produced is reduced. This rapid reduction in post-exercise sweating is dependent on the residual heat load, however non-thermal factors associated with baroreceptor loading status have an overriding influence on sweating response (Mekjavic & Eiken, 2006; Nadel, 1986). Sweating after exercise has been shown to be dependant on changes in blood pressure as well as the intensity of exercise which precedes the recovery (Nielsen et al., 1984). Sweat rate has been shown to be influenced by skin temperature, and the air next to it which creates a gradient for heat transfer (A. P. a. N. Gagge, Y., 1977). During hot humid conditions, sweat rate may not change, but it does become less effective as a means for heat loss because evaporation of sweat becomes difficult without a large gradient between water vapor pressures in the sweat on the skin and the moisture in the air (Gonzalez et al., 1974; Kenney & Zeman, 2002; Webb, 1995). In these instances, heat loss through radiation and conduction/convection through the skin becomes the primary avenue for heat removal from the body (A. P. Gagge & Hardy, 1967; Kenney & Zeman, 2002).

2.0.6 Non-thermal influences on core temperature

Non-thermal mechanisms, such as baroreceptors, are sensitive to changes in blood volume and pressure, while mechanoreceptors and metaboreceptors are sensitive to the stimulation of afferent nerves within skeletal muscle (Nadel, 1986). These non-thermal receptors can vary greatly in their contribution to heat loss processes depending on the amount and types of heat stress on the body. For example, during exercise, barorecptors have been purported to have little or no influence on sweating compared to

mechanoreceptors and metaboreceptors which are mediated by central command through the hypothlamus (Nadel et al., 1971b; Shibasaki et al., 2006b). Mechanoreceptors and metaboreceptors play a large role at the onset of dynamic exercise (Charkoudian, 2003; Kellogg, 2006; Nielsen et al., 1984). There are differences in the relative contribution of non-thermal factors in modulating sweating when comparing dynamic and static exercise, or when comparing thermoneutral and hot ambient conditions –however these concepts are beyond the scope of this research, and the reader is therefore advised to consult the references in this section (Nadel et al., 1971a; Wyss et al., 1974).

As mentioned above, there are multiple mechanisms which control heat exchange in order to maintain core body temperature. Both sweating and SkBF can respond immediately to even the slightest local heat stimulus, while active vasodilation and enhanced sweating efficiency require stronger stimuli and are slower to react or induce significant changes to the body in order to facilitate heat exchange (Sigal *et al.*, 2007). Most often, the non-thermal mechanisms tend to react to strong or immediate efferent stimuli (like hot water touching the skin), whereas the thermoregulatory mechanisms contribute more prominently during endothermic situations which cause changes in T_{core}, -such as long duration exercise (Dean, 2008).

2.1 Diabetes overview

Multiple research studies suggest that individuals with diabetes may be at an increased risk for heat stress and superficial injuries due to decreased thermal sensitivity of the skin (Ijff et al., 1991; Ohtsuka et al., 1995), reduced SkBF and cutaneous vasodilation (Stansberry et al., 1999; Wick et al., 2006; Williams *et al.*, 1996), reduced sweating (Gibbons, 2009; Petrofsky *et al.*, 2008), and decreased sudomotor rhythm

(Petrofsky et al., 2005a; Sun et al., 2008). A majority of these impairments are suggested to be caused by underlying nerve damage (Gibbons, 2009; A. Vinik *et al.*, 2006; A. I. Vinik et al., 2001) which is very common in individuals with diabetes. According to the PHAC, "approximately half of the individuals who develop diabetes experience problems with the transmission of nerve impulses. Ranging from mild to severe, these complications can produce disabling conditions such as impaired sensation, pain in the feet and hands, [...and] other problems of the nervous system," (Public Health Agency of Canada, 2008). Possible causes of nerve impairment have been suggested to include long term: hyperglycemia, hyperinsulinemia, and insulin resistance (Frier, 2002; B. A. Perkins & Bril, 2002; Shun et al., 2004; A. I. Vinik et al., 1992). When individuals with T2DM or pre-diabetes live with these complications for an extended period of time, they often develop peripheral or autonomic neuropathy (Frier, 2002; Resnick *et al.*, 2002; A. I. Vinik et al., 2001).

2.1.1 Alterations in heat loss mechanisms

There are numerous studies showing the physiological similarities and differences between individuals with and without diabetes in response to heat stress or exercise. Most of these studies have focused on local changes in skin blood flow and sweating (Petrofsky et al., 2005a; Williams et al., 1996). Wick (2006) found a significantly delayed threshold for the onset of cutaneous vasodilation during passive heating in participants with T2DM compared to healthy controls (Wick et al., 2006). This meant that the group with diabetes had to reach a higher T_{core} than the control group in order to have a substantial increase in SkBF and a consequent increase in the potential for heat loss. Petrofsky also demonstrated impaired heat loss capacity in participants with T2DM

(Petrofsky et al., 2005a). His study showed a reduced sweat rate and decreased sweat production during physical exercise in the heat (Petrofsky et al., 2005a; Petrofsky *et al.*, 2005b).

Individuals with T2DM may experience impaired heat loss due to various reasons, however, the most common factor associated with reductions in the capacity to dissipate heat is nerve damage (Shun et al., 2004; A. I. Vinik et al., 2001) due to prolonged hyperinsulinemia and hyperglycemia (Levy et al., 1989; B. A. Perkins et al., 2001). It has been shown that in some individuals with T2DM, the nerves that dilate blood vessels are impaired (Hamdy *et al.*, 2001; Sun et al., 2008). Changes in the ability to increase skin perfusion are suspected to impair whole body heat loss because the volume of blood that reaches the skin surface is reduced. Whenever there is a reduction in SkBF, there is a reduction in cooling potential because if warm blood is unable to be brought to the skin's surface to dissipate heat, it is recycled back into the body core where it can increase or maintain an already elevated core temperature.

2.1.2 Common co-morbidities of T2DM

While obesity does not necessarily cause dysfunction of SkBF or sweating directly, having an increased body-surface-area-to-mass ratio (as most individuals with T2DM have) does make an obese individual more susceptible to heat gain from a hot environment (Havenith, 1995; G. Kenny, Yardly, J., Brown, C., Sigal, R.J., Jay, O., 2009). The reason an obese person has a smaller surface area to mass ratio is because their difference in body weight is not proportional to the difference in surface area (DuBois & DuBois, 1916). A bigger person has more mass and they also have a greater surface area, but the changes in the two are not proportional so the ratio is less. This is

important because surface area is the interface across which the body exchanges heat with the environment.

Obese individuals are also at a disadvantage because fat acts as an insulator which impairs heat transfer thereby enhancing the rate of core temperature increase and increasing the rate of body heat storage, leaving the obese individual at an increased risk for heat injury or illness. Because the average specific heat capacity of an obese body is very likely to be less than that of a lean body, there is less heat energy required to raise the body temperature of the obese body: The specific heat capacity of adipose tissue is less than that of fat-free mass (2.97 kJ.g-1.°C as compared to 3.64 kJ.g-1.°C) (Faber & Garby, 1995). Therefore, if the same amount of heat energy is absorbed by an obese and a lean person of the same weight/size, the T_{core} will likely be greater in the person with more fat relative to the leaner person who maintains the heat within the muscles and distributed throughout the body rather than at the core (Faber & Garby, 1995; Havenith & Middendorp, 1990; McLellan et al., 2009).

Sweating may also be reduced in obese individuals, with and without T2DM, due to a reduced ratio of sweat glands-to-body-surface-area (Randall, 1946). Some researchers believe that genetically, all humans are born with a finite number of sweat glands, lending to the conclusion that obese individuals have a reduced capacity for evaporative heat loss relative to a smaller, non-obese individual (Randall, 1946; Wilke et al., 2007). These changes in obesity leave individuals with a reduced heat loss capacity, enhanced heat production and conservation, and an overall risk of prolonged elevated T_{core}.

New research has provided some insight on how body fat and skin thickness affects thermoregulation in individuals with type 2 diabetes. Recently, Petrofsky et al

(2008) noted a marked reduction in skin thickness, skin blood flow, and decreased skin temperature in older individuals compared to a younger control group (Petrofsky et al., 2008). These differences were exacerbated in the older group with diabetes. Researchers have speculated that the reduced skin blood flow may be due to a reduction in capillaries in the skin simply caused by a decrease in the amount of skin covering the body (McLellan et al., 2009), which is likely to impair skin heat dissipation in older individuals with diabetes.

Hypertension, which is often found in obese individuals with T2DM, is purported to impair vascular reactivity due to the contraindications of hypertension itself, such as sympathetic over-activity (Jaap *et al.*, 1994). Though the mechanisms have yet to be elucidated, it has been shown that, at rest and during local heating, hypertensive individuals have reduced skin blood flow (Carberry *et al.*, 1992; Kenney & Kamon, 1984). Kenney (1984) showed reduced forearm blood flow and skin blood flow in hypertensive individuals during exercise in the heat (Kenney, 1985; Kenney & Kamon, 1984). Jaap (1994) found reductions in maximal forearm blood flow which were similar in both hypertensive and normotensive individuals with T2DM compared to non diabetic normotensive controls (Jaap et al., 1994). He also found that hypertensive individuals with T2DM showed greater resistance to flow than normotensive individuals with T2DM, indicating that the cumulative effect of hypertension and T2DM is more detrimental than each individual disease.

Reductions in vasodilatory capacity, such as those found in hypertension, are purported to arise as a result of nerve damage to C-fibres -due to prolonged hyperinsulinemia or elevated blood glucose levels - which is expressed most commonly as peripheral or autonomic neuropathy (B. A. Perkins et al., 2001; Shun et al., 2004; A. I.

Vinik et al., 2001). Many studies have shown that nerve damage is manifested by a reduction in innervation to the skin and sweat glands, (Gibbons, 2009; Hamdy et al., 2001; Kennedy & Wendelschafer-Crabb, 1996; A. I. Vinik et al., 2001). Shun et al. (2004) found that the density of Intra-Epidermal Nerve Fibres (IENF) was significantly reduced in T2DM (1.0 vs. 9.0 fibres/mm in T2DM vs. healthy controls), which may result in a reduced capacity to stimulate sweat glands by means of fewer and less intense pulses of sudomotor nerve activity (Shun et al., 2004).

Damage to blood vessels, and the nerves that innervate them, are also suspected of being responsible for impaired active cutaneous vasodilation (Gibbons, 2009; Hamdy et al., 2001; A. I. Vinik et al., 2001). This type of damage is purported to cause a decrease in vasodilatory ability –especially impairing SKBF- which leads to decreased skin perfusion and therefore a decreased potential to move heat away from the body core. Overall, this type of impairment implies a reduced capacity to create a temperature gradient which is large enough to effect sufficient dry and evaporative heat loss. Healthy, functional nerves are vital for the control of SkBF and sweating. These physiological reactions are essential to facilitate the necessary increase in evaporative heat loss during and after exercise, or during heat stress. Therefore, body heat storage is greatly affected by the capacity and adaptability of SkBF and sweating.

2.2 Summary

The most prominent complications that may impair heat loss include hypertension, hyperinsulinemia, an advanced-aging process, T2DM, and obesity. It has been suggested that altered local heat loss mechanisms will create less efficient whole body thermoregulation, especially when under multiple stresses such as exercise in a hot

humid environment. However, the majority of current findings related to impaired heat loss mechanisms in individuals with T2DM have been expressed primarily in terms of local physiological changes. This has left a gap in current literature because none of these local changes have been expressed in terms of their effects on changes in whole body heat dissipation or body heat content.

CHAPTER III

Methodology

3.0 Participants

Subsequent to approval of the experimental protocol by the University of Ottawa Human Research Ethics Committee, participants between the ages of 45 and 65 years old were recruited to participate in this study. Special approval was also granted by the Ottawa Hospital Ethics Board to use the Diabetes Aerobic and Resistance Exercise (D.A.R.E.) study (Sigal et al., 2007) database from which to contact potential participants with type 2 diabetes. (See Appendix B for Telephone protocol for contacting DARE participants).

Seven participants with type 2 diabetes (T2DM group) and 7 non-diabetic individuals (CON group) completed all screenings and both trials. The control group consisted of healthy (no history of respiratory, metabolic, cardiovascular, or diabetes and not currently on any medication that treats these complications) male and non-pregnant females who had not been heat acclimated. These same criteria applied to the T2DM group; however individuals must have been diagnosed with T2DM for at least 5 years according to the Canadian Diabetes Association Guidelines (Dean, 2008).

Participants in the T2DM group were permitted to control their diabetes with diet, exercise, oral anti-hyperglycaemic agents, or any combination of these treatments; However, those using insulin were not allowed to participate. Due to suspected reductions in thermoregulatory capacity associated with nerve damage and the possible dangers of heat illness/injury due to the study protocol, we only selected participants who were free of nerve-related dysfunction or disease as assessed by their family physician and/or endocrinologist and by our researchers who performed monofilament testing.

Participants must have answered no to all screening questions related to having ever been diagnosed with autonomic neuropathy, nephropathy, retinopathy or any other sensation loss AND these problems must have been ruled out by their doctor within the last year. Participants in both groups were non-smokers (or quit for at least 7 years) and none were exposed to second hand smoke on a regular basis.

We tried to match all participants for physical fitness levels (VO_2 ml/kg/min), age, percentage of body fat, and body surface area (BSA) in order to minimize the potential differences in heat exchange capacity between groups. Body surface area was calculated from the measurements of weight and height according to Du Bois (DuBois & DuBois, 1916).

3.0.1 Inclusion criteria

Participants must have **No**:

1) Uncontrolled hyperglycaemia (fasting plasma glucose must not be greater than > 5.9 mmol/L for healthy individuals, and must be greater than or equal to 7.0 but not higher than 11.0 mmol/L for individuals with type 2 diabetes - without taking medications before blood draw) . Control group must have A1c < 6.0 % and type 2 diabetes subjects must have A1c > 6.0 but < 10.0 %.

2) Changes in medications for diabetes, blood pressure or lipids in the two months prior to enrolment nor during testing.

3) Significant weight or body composition change (an increase or decrease of more than 2 kg of body weight during the three months before start of experimental trials).

4) Significant renal disease. (serum creatinine > 150)

5) Uncontrolled hypertension (systolic blood pressure >140 mmHg; diastolic BP >90 mmHg, measured in a sitting position; or no history of severe syncope

6) Restrictions in physical activity due to disease: intermittent claudication, severe peripheral neuropathy or active proliferative retinopathy, unstable cardiac or pulmonary disease, disabling stroke, significant musculoskeletal injury, or severe arthritis.

7) Other illness that would make participation in this study inadvisable as judged by the patient's and our own physicians.

3.0.2 Exclusion criteria

These exclusion criteria were designed to limit participation to relatively healthy people with or without T2DM, and to avoid unnecessary complications that may occur during exercise or prolonged exposure to heat or stress on the body. The following criteria are also designed to screen out individuals who are at a higher risk for injury, or those who may be acclimatized to heat due to intense physical training or repeated/frequent exposure to hot environments.

Participants must **not:**

-be exposed to high temperatures on a regular basis

-have severe clinically diagnosed neuropathies (i.e. unstable proliferative retinopathy or autonomic neuropathy)

-be excessively obese (body fat greater than 55% by DEXA)

-have uncontrolled hypertension

-use insulin to control diabetes

-have been diagnosed with end-stage renal (or other kidney) disease

-have uncontrolled asthma

-have a VO_{2max} greater than 35 ml/min/kg in women and 40 ml/min/kg in men

-have any uncontrolled contagious illness or disease

3.1 Protocol

The study consisted of a series of pre-screenings, one familiarization session and two experimental sessions. Participants were screened via telephone interview and physical examinations (described below) to rule out co-morbidites, including clinically relevant neuropathy, excessive obesity (body fat >55%), and history of cardiovascular disease. Participants reported to the Laboratory for Human Bioenergetics and Environmental Physiology on three separate days; to the Montfort Hospital on another day and any Gamma Dynacare Clinic on any morning of their choosing 1-2 weeks before testing began. Informed consent was obtained from each potential participant before any procedures took place.

3.2 Pre-screening

This initial point of contact was performed on the phone, in person, or via email, depending on the participants' convenience. This screening was undertaken to 1) ensure that participants met all inclusion criteria; 2) to discern whether or not they were interested in participating in the whole study; and 3) explain the difficulties of the study to see if they thought they would be able to physically and mentally overcome the stresses during testing. If all of these conditions were met, participants taking medications were invited to come to a familiarization session. Potential participants were asked to bring a prescription summary or pill bottles when they came for their first visit.

3.3 Familiarization session

This session was conducted in order to familiarize the participant with all measurement techniques and protocol details being performed during the trials. This also provided the participant with the opportunity to ask any questions regarding the experiment. The participants were asked to complete a Physical Activity Readiness Questionnaire (PAR-Q) (104), an International Physical Activity Questionnaire (IPAQ) (105), and a Participant Information Package created specifically for this study. These questionnaires helped assess general physical health, evaluate the participants' readiness for exercise, and assess their current level of physical activity.

At the end of the information session, we gave the participant the opportunity to read the Background and Informed Consent document. If they agreed to take part in the study, they were then asked to sign the aforementioned document. Thereafter, the co-investigator completed some basic measurements including height, weight, resting blood pressure, and 2-hr post-prandial glucose.

At the end of this preliminary session, participants were asked to attend two screening appointments; one for blood sampling at any Gamma-Dynacare laboratory in Ottawa or Hull, and one for a VO_{2max} stress test at Montfort Hospital.

3.3.1 Screening visit #1

The purpose of this visit was to obtain fasting blood samples from potential participants. Qualified candidates were asked to fast for 12 hours overnight and refrain from taking any medications until after giving the blood sample. Levels of fasting blood glucose, % Hb_{A1c}, creatinine, and albumin were tested.

3.3.2 Screening visit #2

The purpose of this visit was to conduct the VO_{2max} stress test and determine body adiposity. A modified Bruce protocol was used on an upright cycle ergometer for the test. After one minute of resting data, participants performed one minute of warm-up by pedalling with no work load. Each subsequent minute after warm-up, participants were subjected to a 15-25 watt increase in resistance while maintaining 60 revolutions per minute. Selection of the warm-up resistance and workload increments were subjective, with the goal of producing exhaustion within 8-12 min. The test was terminated when the participant could no longer maintain the speed, or if there were clinically relevant responses in blood pressure, heart rate, or noticeable contraindications on the ECG.

Body composition was determined using Dual Energy X-Ray Absorptiometry, whereby the body mass was partitioned into fat mass, and fat free mass. This procedure was performed and interpreted by qualified technicians with the assistance of the co-investigator. The coefficient of variation and correlation was not performed for the participants' DEXA scan in this study.

3.4 Experimental trial sessions

For each experimental session, participants were asked to take all medications as usual as prescribed by their physician, especially individuals with T2DM so that problems associated with glucose and insulin imbalances could be prevented. Participants were instructed to avoid caffeine, alcohol, and any exercise for at least 12 hours prior to any testing session. Dietary intake was controlled in all participants for the last meal before each trial. All participants ate 1/3 of their daily calories (formula for

calories: 10 x weight in kg; breakdown: 55% carbohydrate, 25% fat, and 20% protein, between two and four hours before testing began. Participants were instructed to consume between 250-750 ml of water within the four hours before testing started. Participants were instructed to stay out of saunas and hot tubs prior to all screenings and trials (usually a 2-4 week period) in order to avoid heat acclimation, and acute changes in metabolic rate and core temperature. Both trials were performed at the same time of day to avoid influences caused by shifts in circadian rhythm (Aoki *et al.*, 1995). The trials took place in the chamber of the calorimeter, where air temperature, flow, and humidity were controlled and monitored.

All participants measured blood glucose (using our personal glucose meter) upon arrival at the lab, followed by measurements at 10, 30, and 50 minutes of each stage of the trials. If values were near critical levels, more measurements were taken over shorter durations. For all experimentation, clothing was standardized at ~0.2 to 0.3 clo (i.e. cotton underwear, shorts, socks, sports bra or tank bra (for women) and athletic shoes.

Following instrumentation, participants entered the calorimeter set randomly at 24°C or 30°C and a relative humidity of 30-50%, and began a 60-min habituation period in a recumbent position. Participants then began cycling on the recumbent constant load cycle ergometer at ~55% of their VO_{2max}. Exercise stopped after 60 minutes and was followed by a 60-minute resting recovery in the recumbent position. Immediately following the 60 minute recovery period, local forearm heating (to 44°C) was performed to induce maximum blood flow. This lasted from 20 to 45 minutes, depending on the subject's responsiveness to the heating protocol. Heating was terminated, along with the trial, once SkBF reached steady state values and remained elevated for at least five minutes.

Oxygen consumption and heart rate were measured constantly throughout baseline rest, exercise and recovery. Blood pressure was taken by the automated cuff every 10 minutes during rest, exercise and recovery, and was taken every five minutes during local forearm heating. If values appeared abnormal, a second reading was performed one minute later.

To compare levels of heat and exercise perception, we used thermal sensation and perceived exertion scales throughout the experimental sessions. Participants were asked every ten minutes to choose a number from the perception-based heat strain index (106) and during exercise, they were asked to look at the Borg Scale of perceived exertion (107) and read their level of exertion out loud over the intercom. The use of these perception-based scales has been shown to be sensitive to exercise tolerance, and fitness level, such that those with higher VO_{2max} scores report lower scores than less fit individuals, likely due to heat acclimation which occurs with regular exercise training (106).

3.5 Instrumentation

3.5.1 Thermal and cardiovascular measures

Rectal temperature (T_{re}) was measured by placing a paediatric thermocouple probe of approximately 2 mm in diameter (Mon-a-therm General Purpose Temperature Probes, Mallinckrodt Medical, St-Louis, MO, USA) to a depth of 10-12 cm past the external anal sphincter.

Skin temperature was measured at four points over the body surface using 0.3 mm diameter T-type (copper/constantan) thermocouples integrated into heat-flow sensors (Concept Engineering, Old Saybrook, CT, USA). Thermocouples were attached to the

skin surface with hypoallergenic surgical tape (Blenderm, 3M, St. Paul, MN, USA). Mean skin temperature (T_{sk}) was calculated using 4-point skin temperatures weighted to the regional proportions as follows: (Chest•0.3)+(Trap•0.3)+(Quad•0.2)+(Calf•0.2)

Local temperature data (core and skin) was collected using an HP Agilent data acquisition module (model 3497A) at a sampling rate of 10 s and was simultaneously displayed and recorded in spreadsheet format on a personal computer (IBM ThinkCentre M50) with LabVIEW software (Version 7.0, National Instruments, TX, USA).

Heart rate (HR) was monitored using a Polar coded transmitter, recorded continuously and stored with a Polar Advantage interface and Polar Precision Performance software (Polar Electro Oy, Finland). Participants were also asked to read HR aloud over the intercom throughout the experimental sessions.

Blood pressure was measured both manually, (during screenings) by an automated machine at the level of the heart with an appropriate sized cuff. The automated machine which was used during the experimental sessions required the participant to press the start button and read results out loud over the intercom system. These recordings were also saved electronically in the automated system for later retrieval.

Local sweat rate (LSR) was measured using a 5.0 cm^2 ventilated capsule placed over the medial inferior aspect of the right trapezius muscle. Anhydrous compressed air was passed through the capsule and over the skin surface (Brooks 5850, Mass Flow Controller, Emerson electric, Hatfield, Pa, USA). The vapour density of the effluent air was calculated from the relative humidity and temperature measured using the Omega HX93 humidity and temperature sensor (Omega Engineering, Stanford, CT, USA) and a precision dew point mirror (RH Systems model 373 H, Albuquerque, NM, USA). Local sweat rate was calculated as the product of the difference in water content between

effluent and influent air and the flow rate. The flow rate through the capsule was set to 1.0 $L \cdot min^{-1}$. The sweat rate value was adjusted for skin surface area under the capsule and expressed in $mg \bullet min^{-1} \bullet cm^{-2}$.

Skin blood flow was measured by laser-Doppler velocimetry (PeriFlux System 5000, main control unit; PF5010 LDPM, Function unit; Perimed, Stockholm, Sweden) from the left mid-anterior forearm. The laser-Doppler flow probes (PR 401 Angled Probe; Perimed) were taped to cleaned skin at the left mid-anterior forearm in a region devoid of large superficial veins and from where consistent readings were noted using mapping techniques outlined by Mack et al . The heater on the Laser Doppler was set at 34°C during the trial and at 44°C during local heating after the trial, (See Protocol: *Experimental trial sessions* for a full description of heating procedure). Skin blood flow measures were expressed as a percentage of Max SkBF, and were used to derive an index of cutaneous vascular conductance (CVC). Cutaneous vascular conductance was calculated by using minute-averages of SkBF divided by mean arterial pressure (MAP). Cutaneous vascular conductance was normalized by expressing the changes over time as a percentage of the maximal values achieved during local heating to 44°C as measured at the end of the experimental session. Maximal values of SkBF were acquired by taking an average of five minutes of stable SkBF values once was a plateau was reached during local forearm heating.

An Electrocardiogram (ECG) was performed by a qualified technician during the VO_{2max} stress test to screen for cardiac abnormalities. This enabled the investigators to reduce the risks of a cardiac event by excluding individuals who test positive for abnormalities.

3.5.2 Whole body calorimetry

The modified Snellen direct air calorimeter was employed for the purpose of measuring the rate of evaporative heat loss (H_E) and dry heat loss (H_D), yielding an accuracy of ± 2.3 W for the measurement of rate of total heat loss. A full peer-reviewed technical description of the fundamental principles and performance characteristics of the Snellen whole body calorimeter is available (Reardon et al., 2006).

In brief, the calorimeter incorporates a semi-recumbent constant load eddy current cycle ergometer. The ergometer pedals were located inside of the calorimeter and mechanically linked by chains to the resistance control unit outside of the calorimeter so that any heat generated by the unit does not enter the calorimeter. The calorimeter was housed within a climatic chamber slightly pressurized (+8.25 mmHg) to nullify potential air leakage through the calorimeter walls. Differential air temperature and humidity were measured above the calorimeter by sampling the influent and effluent air. The water content was measured using precision dew point thermometry (RH Systems model 373H, Albuquerque, NM, USA), while the air temperature was measured using RTD high precision thermistors (± 0.002°C, Black Stack model 1560, Hart Electronics, UT, USA). Air mass flow through the calorimeter was estimated by differential thermometry over a known heat source (2 x 750 W heating elements) placed in the effluent air stream. Differential temperature over the heater was measured using a third aforementioned high precision thermistor placed down-stream from the heater. Air mass flow rate (kg air • min^{-1}) was continuously measured during each trial. Data from the calorimeter was collected continuously at 8 s intervals throughout the trials. The real time data was displayed and recorded on a personal computer (Dell OPTIPLEX GX270) with LabVIEW software (Version 7.0, National Instruments, TX, U.S.A). The calorimeter

was calibrated for rate of dry heat loss using a humanoid manikin heat source made of constant power zone heater cable (5.905 $k\Omega \cdot m^{-1}$, Easy Heat ZH8-1CBR, New Castle, IN, USA); and for rate of evaporative heat loss using a precision tubing pump (Cole-Palmer, Masterflex 7550-30; Pump head 77200-50) delivering 5 $ml \cdot min^{-1}$ (± 0.01 $ml \cdot min^{-1}$) of water to a heated 1200 watts hotplate.

H_E was calculated from the calorimetry data every minute using the following equation:

$$H_E = \frac{(Massflow \bullet (Humidity_{out} - Humidity_{in}) \bullet 2427)}{60} \text{.....Watts.....} (2)$$

-where mass flow is the rate of flow of air mass (kg air$\cdot s^{-1}$);

($Humidity_{out}$ – $Humidity_{in}$) is the calorimeter outflow-inflow difference in absolute humidity (g water • kg air^{-1}); and

- 2427 is the latent heat of vaporization of sweat (J • g $sweat^{-1}$) at 30°C.

Dry heat loss (H_D) in the form of radiation, and conduction was calculated from the calorimetry data every minute using the following equation:

$$H_D = \frac{(Massflow \bullet (Temperature_{out} - Temperature_{in}) \bullet 1005)}{60} \text{.....Watts.....} (3)$$

...where mass flow is the rate of flow of air mass (kg air$\cdot s^{-1}$);

-($Temperature_{out}$ – $Temperature_{in}$) is the calorimeter outflow-inflow difference in air temperature (°C); and

- 1005 is the specific heat of air (J• (kg air • °C)$^{-1}$).

3.5.3 Indirect calorimetry

The rate of metabolic heat production (M) was determined by indirect calorimetry, and then the external work rate (W) was subtracted from M to calculate total

metabolic energy expenditure. External work rate (W) was subtracted to exclude the influence of mechanical energy. A 6-litre fluted mixing box housed within the calorimeter was used to determine the rate of metabolic energy expenditure. Expired gas was analyzed for oxygen (O_2) (error of ± 0.01%) and carbon dioxide (CO_2) (error of ± 0.02%) concentrations using electrochemical gas analyzers (AMETEK model S-3A/1 and CD 3A, Applied Electrochemistry, Pittsburgh, PA, USA). Expired air was recycled back into the calorimeter chamber in order to account for respiratory dry and evaporative heat loss. Prior to each session gas mixtures of 4% CO_2, 17% O_2, and 79% nitrogen were used to calibrate the gas analyzers and a 3-litre syringe was used to calibrate the turbine ventilometer (error < 1%). Rate of metabolic energy expenditure was calculated from minute-average values for VO_2 and the respiratory exchange ratio.

The rate of total heat loss was calculated every minute using the sum of H_E and H_D. The rate of body heat storage (S, in kJ) was calculated every minute by subtracting heat loss from (M - W) and the total changes in body heat content (ΔH_b) per period (60 minutes exercise, 60 minutes recovery) were calculated using the following equation:

$$\Delta H_b @ time(t) \equiv \left(\frac{S \times 60}{1000} \right) \text{ ..... kJ/min} \quad \text{.....(4)}$$

3.6 Statistical Analysis

A one-way ANOVA with repeated measures was used to separately analyze the data in exercise and recovery time periods. The repeated factor was time, which had 8 levels for the exercise period (levels: 0, 2, 5, 10, 15, 30, 45, and 60 minutes) and 7 levels for the recovery period (levels: 2, 5, 10, 15, 30, 45, and 60 minutes). The non-repeated factor was the presence of diabetes; (Control vs. T2DM group. The dependent variables were total heat loss, H_E, H_D, heat load, ΔH_b, T_{rec}, and mean T_{sk}. The same test was conducted for SkBF, %CVC max, MAP, SBP, DBP, LSR, and thermal sensation, however the measurement period used for the analysis of these variables were 10, 20, 30, 40, 50, 60 minutes for exercise and recovery separately. Paired t-tests were performed for data that required direct comparison of means between groups, such as residual heat storage, or cumulative heat storage/period. For ANOVA main effects, Huynh-Feldt corrected statistics are reported where the assumption of sphericity was not met. Data were analyzed to determine the differences between trials (within-subject), within groups, and between groups. Whenever a significant difference or interaction was found between any contrasts, post-hoc tests were performed to a significance level of 0.05 and the alpha level was adjusted during multiple comparisons so as to maintain the rate of type 1 error at 5% during Bonferroni post-hoc analysis ($p \leq 0.05 \bullet n^{-1}$; n = number of comparisons). All analyses were performed using the statistical software package SPSS 14.0 for Windows (SPSS Inc. Chicago, IL, USA).

CHAPTER IV

Results

4.0 Participants

Individuals with T2DM were matched with a counterpart from the control group. The goal was to have only a small difference between matched pairs for age (≤ 5 years), height (≤ 5 cm), weight (≤ 10 lbs), % body fat (≤ 3%), VO_{2max} (≤ 400 ml/kg/min) and BSA (≤ 0.05 cm^2); However, this tight matching was not possible due to the limited number of participants who qualified for and participated in this study. Instead, group means were used for all comparative purposes. The only significant differences between groups were those measures which are directly associated with diabetes, such as duration of diabetes; 9.4 ± 3.2 years vs. no diabetes, ($p = 0.0001$) and HbA1c; 7.5 ± 1.2 % vs. 5.3 ± 0.4%; both of which were higher in the T2DM group compared to the CON group respectively.

Table 1. Subject demographics compared by group mean

	Control	Type 2 diabetes	P-value
Age (years)	53 (6.4)	56 (6.2)	0.17
Number of males/females	2/5	4/3	-
Height (m)	1.66 (0.096)	1.70 (0.095)	0.25
Weight (kg)	80.5 (12.7)	91.5 (8.7)	0.08
Fat free mass (kg)	31 (8.7)	34 (5.5)	0.45
% body fat	38.5 (8.9)	37.5 (7.2)	0.86
VO_{2max} (L/min)	2.024 (0.44)	2.015 (0.45)	0.97
VO_{2max} (L/kg FFM/min)	0.070 (0.025)	0.061 (0.020)	0.24
HbA1c (%)	5.3 (0.4)	7.5 (1.2)	0.0019*
Diabetes duration (years)	---	9.4 (3.2)	0.0001*
BSA (cm^2)	1.89 (0.20)	2.03 (0.15)	0.18

* indicates significant difference between groups; FFM, fat free mass; BSA, body surface area

4.1 Calorimetry data

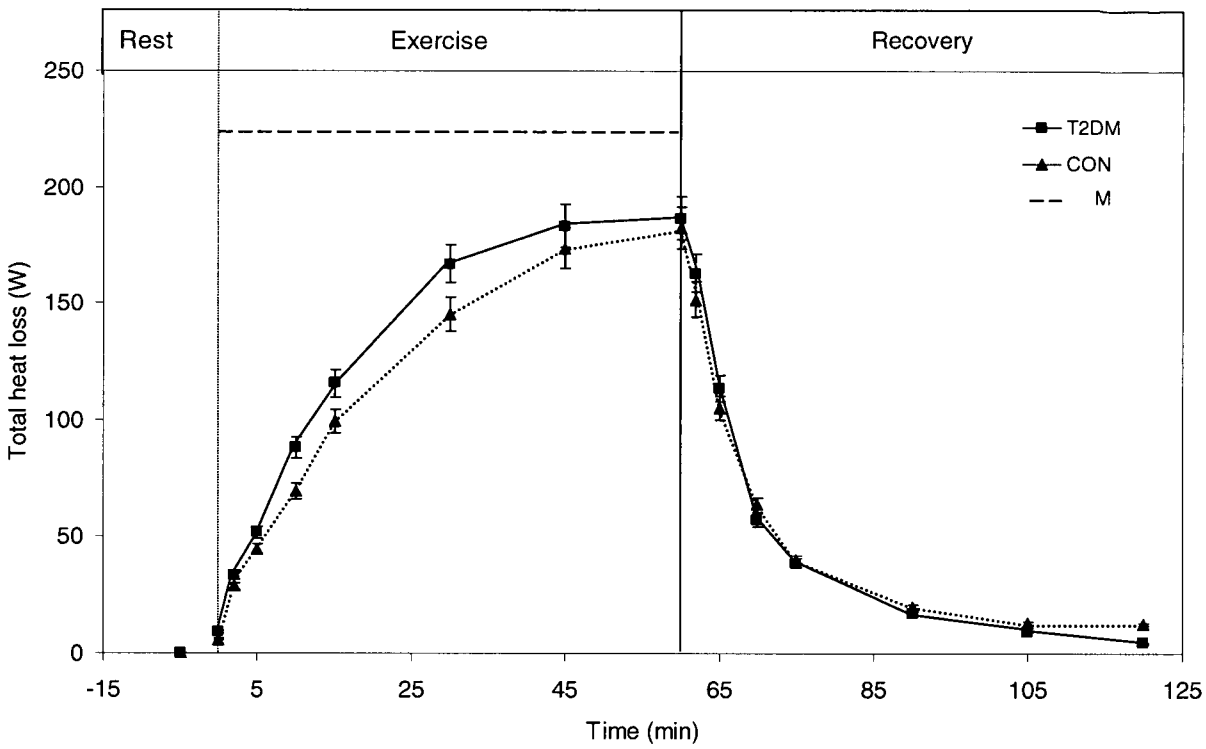
Temperate conditions (24°C)

At 24°C, the mean heat load during exercise – taken as the average heat load over the last 30 minutes - was not significantly different between groups (p=0.23), where the T2DM group averaged 335 ± 63 watts and the CON group averaged 308 ± 68 watts. Total heat loss (Panel A) and the rate of heat storage (Panel B) did not vary significantly between groups at any time point during exercise or recovery ($p > 0.09$ for all points), (See Figure 1).

There was no main effect of group on H_E during exercise, however there was a significant effect of time ($p<0.001$), indicating that both groups had parallel changes in heat loss over the exercise period, as can been seen in Figure 2. The average H_D was not different between groups during exercise (p=0.34), however there was again, a significant effect of time; p=0.047, (See Figure 2).

Evaporative heat loss was not different between groups during the recovery period, however there was a significant effect of time, (p=0.005) indicating that both groups had parallel changes in heat loss over the recovery period, as can been seen in Figure 2. The mean H_D was not different between groups (p=0.96) during recovery, however there was a significant effect of time (p=0.004); (See Figure 2).

A



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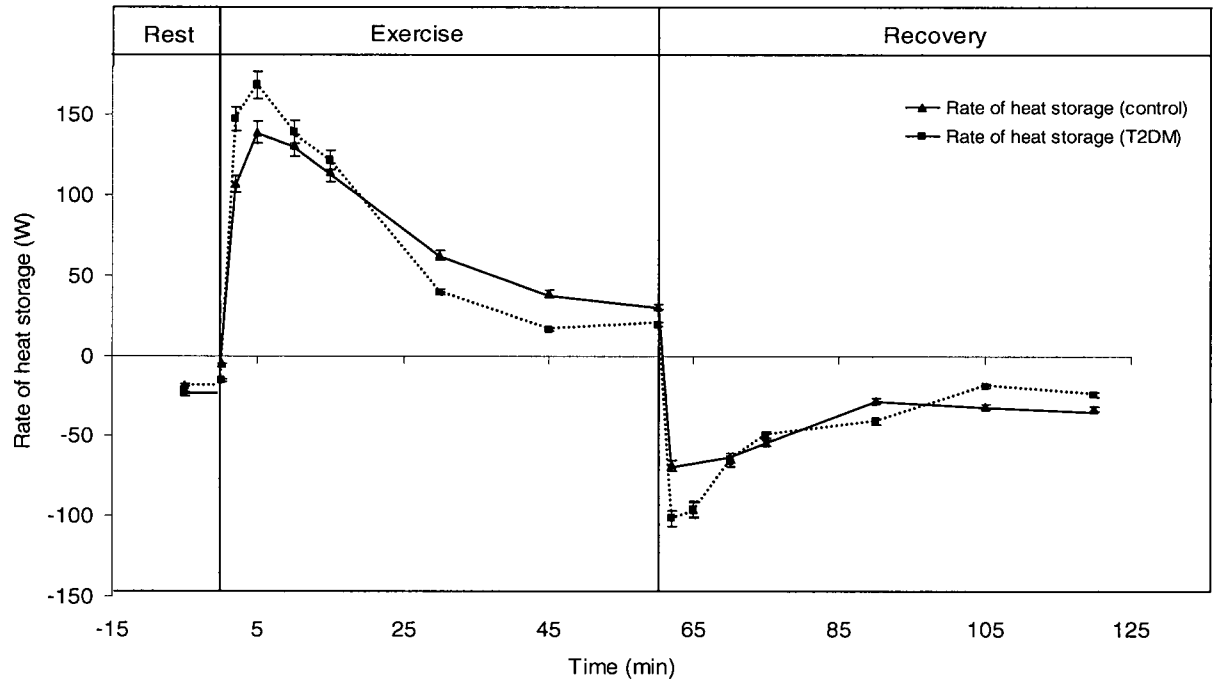


Figure 1. Total heat loss (evaporative + dry) (Panel A) and rate of heat storage (Panel B) at 24°C. Values are group means at baseline, during 60 min of cycling, and during 60 min of inactive recovery. Values in Panel A are relative to baseline levels of metabolic heat production. T2DM = type 2 diabetes mellitus group; CON = control group; M = average metabolic heat production during exercise.

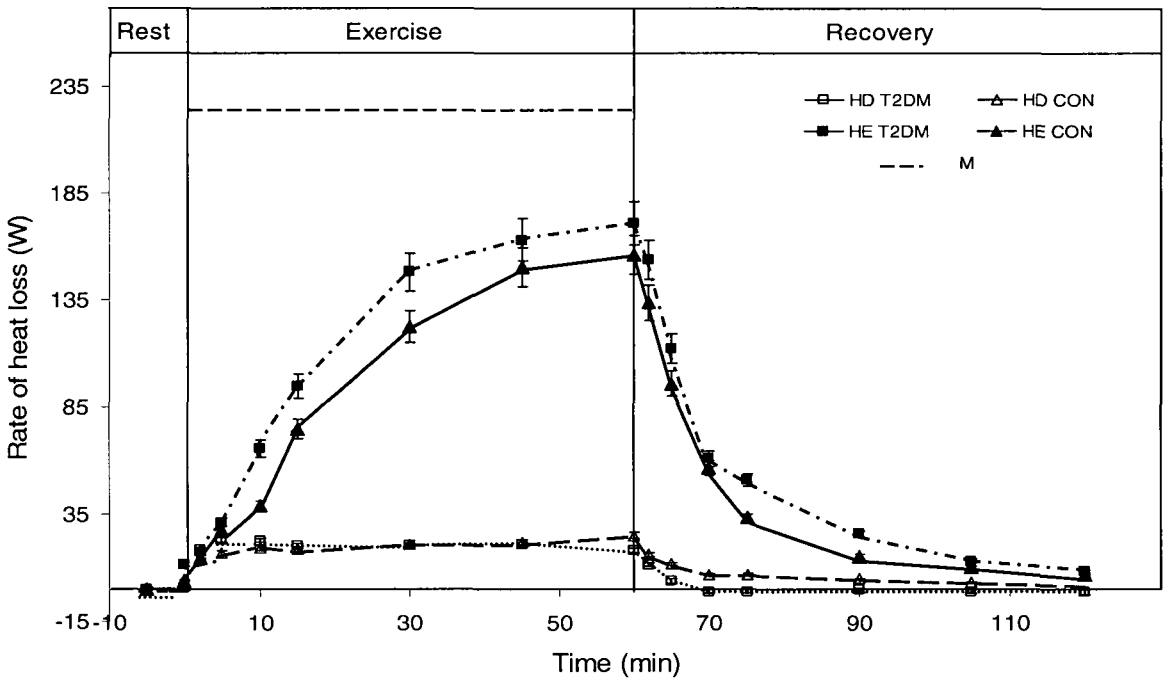


Figure 2. Mean whole body evaporative heat loss (H_E) and dry heat loss (H_D) in 24°C. Comparison at baseline, during 60 min of cycling, and during 60 min of inactive recovery. Values are relative to baseline levels of metabolic heat production.

During exercise, the ΔH_b was + 247 ± 44 kJ and + 266 ± 72 kJ for the T2DM and CON groups respectively (p=0.29). During recovery, no differences in heat loss were observed between groups, where ΔH_b was -156 ± 41 vs. -129 ± 66 kJ in T2DM and CON respectively, p=0.38). However, a significant difference in residual heat storage (calculated as ΔH_b from exercise minus ΔH_b from recovery) was observed between groups, (p=0.042). The T2DM group lost 63 ± 12% of the heat gained during exercise (residual heat storage: +91 ± 36 kJ) compared to the CON group who lost only 46 ± 15% of the heat they gained, (residual heat storage: +137 ± 30 kJ); p=0.047, (See Figure 3).

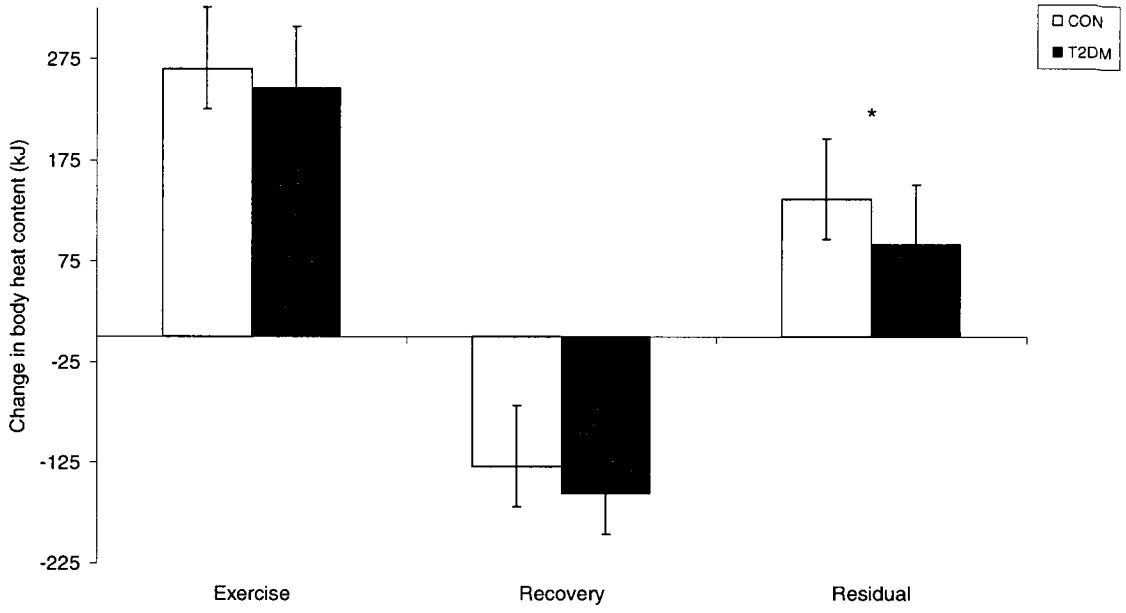


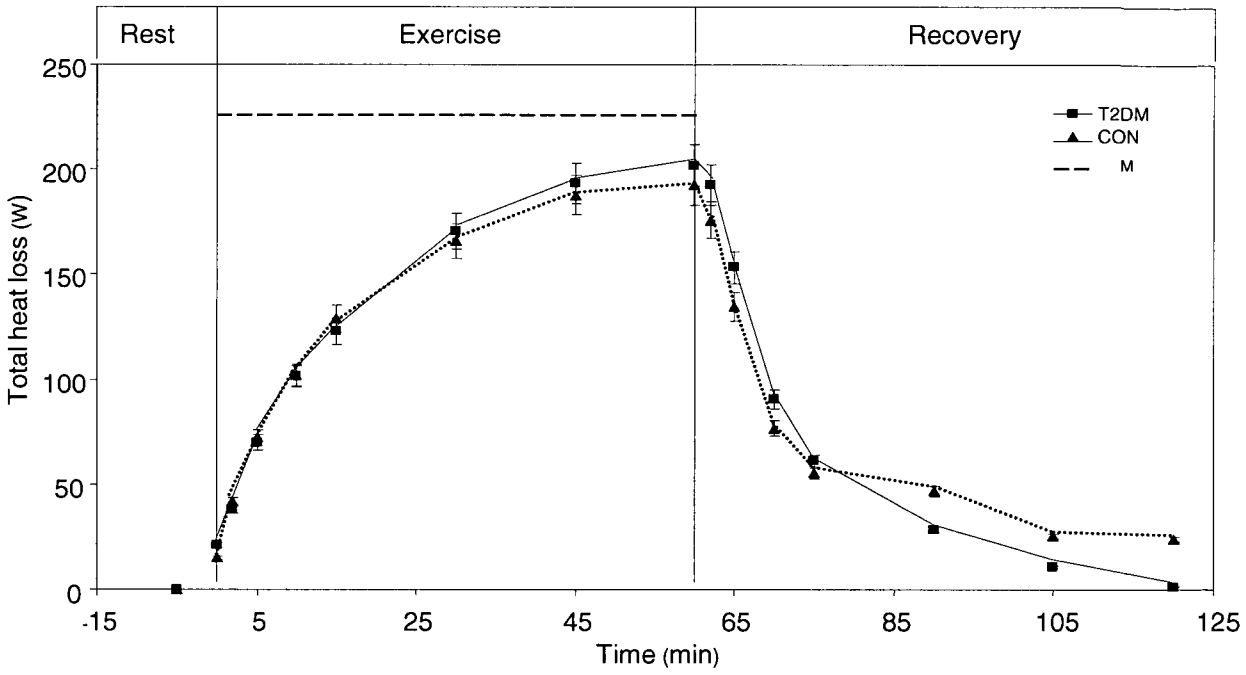
Figure 3. Changes in body heat content at 24°C. Values are group means presented as: total heat gained during exercise, total heat lost during recovery, and the residual heat stored by the end of the trial (ΔH_b from exercise minus ΔH_b from recovery). CON =control group; T2DM= type 2 diabetes group.* indicates significant difference between groups

Hot conditions (30°C)

At 30°C, mean heat load during exercise was not significantly different between groups 346 ± 68 vs. 311 ± 73 W, p=0.19 at 30°C (T2DM vs. CON) (See Figure 4). Total heat loss (Panel A) and the rate of heat storage (Panel B) did not vary significantly between groups at any time point during exercise or recovery ($p > 0.09$ for all points), (See Figure 4).

The mean H_E was not different between groups during exercise, however there was a significant effect of time for all trials, p=0.002 indicating that both groups had parallel changes in heat loss over the exercise period, as can been seen in Figure 5. There was no significant difference in H_D for time (p= 0.33) or diabetes status (p=0.62) at any time during the exercise period (See Figure 5).

A



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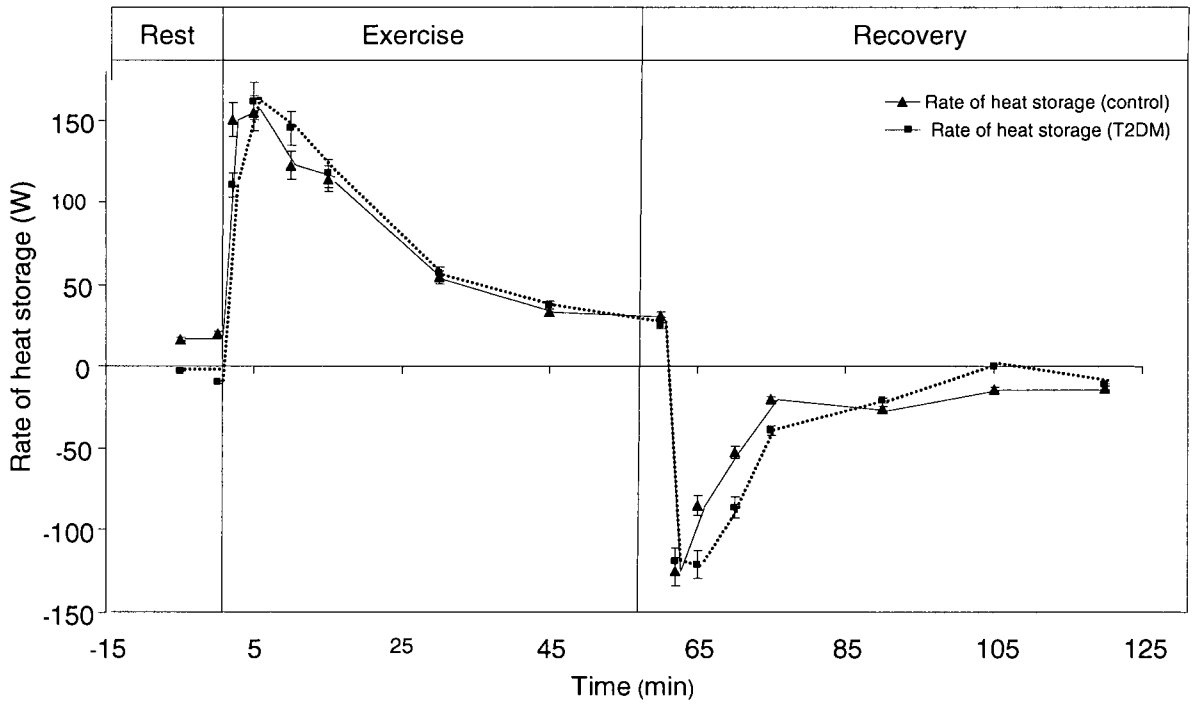

Figure 4. Total heat loss (evaporative + dry) (Panel A) and rate of heat storage (Panel B) at 30°C. Values are group means at baseline, during 60 min of cycling, and during 60 min of inactive recovery. Values in Panel A are relative to baseline levels of metabolic heat production. T2DM = type 2 diabetes mellitus group; CON = control group; M = average metabolic heat production during exercise.

The mean H_E was not different between groups during the recovery period, however there was an effect of time for all trials, ($p < 0.001$) indicating that both groups had parallel changes in heat loss over the recovery period, as can been seen in Figure 5. The mean H_D was not different between groups during recovery (See Figure 5).

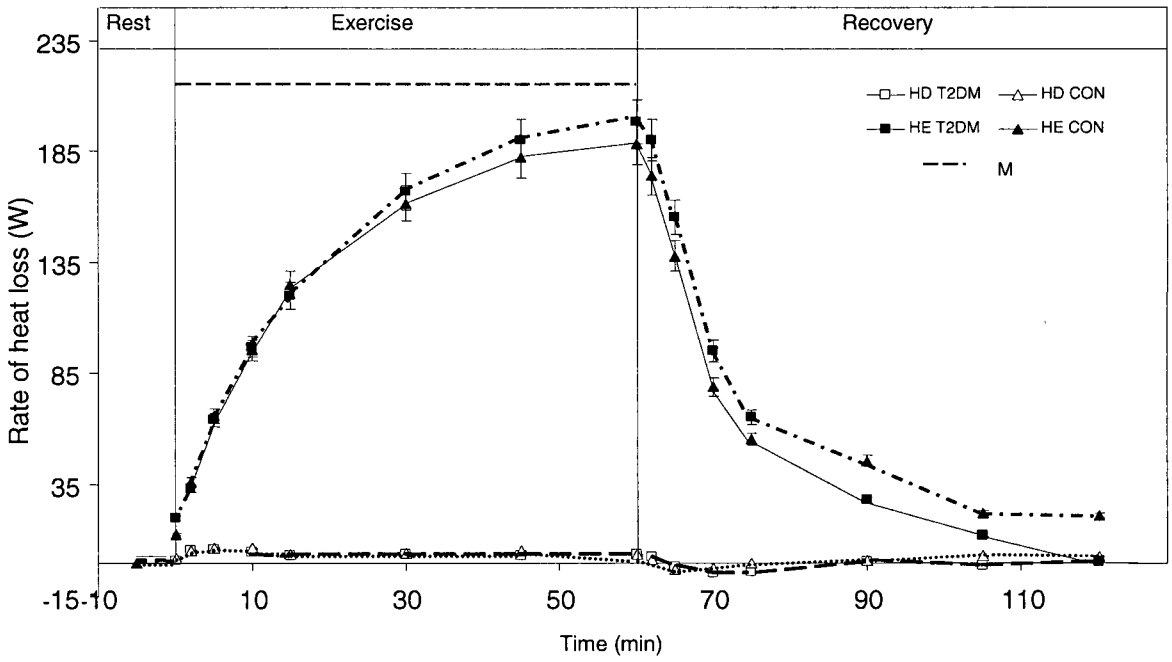

Figure 5. Mean whole body evaporative heat loss (H_E) and dry heat loss (H_D) at 30°C. Comparison at baseline, during 60 min of cycling, and during 60 min of inactive recovery. Values are relative to baseline levels of metabolic heat production.

No difference in ΔH_b was observed between the T2DM and control group during the exercise period (248±30 vs. 260±66 kJ/period, p=0.34). No differences in heat loss were observed during the recovery period (T2DM: -123 ± 38 kJ vs. CON: -111 ± 48 kJ, p=0.63). After the one-hour recovery period, the T2DM group had lost 49 ± 11% of the

heat gained during exercise (residual heat storage: +126 ± 20 kJ) whereas the CON group lost 42 ± 8% of the heat they gained (residual heat storage: +149 ± 31 kJ), which showed a trend towards greater heat loss, but was not significantly different (p=0.073); See Figure 6).

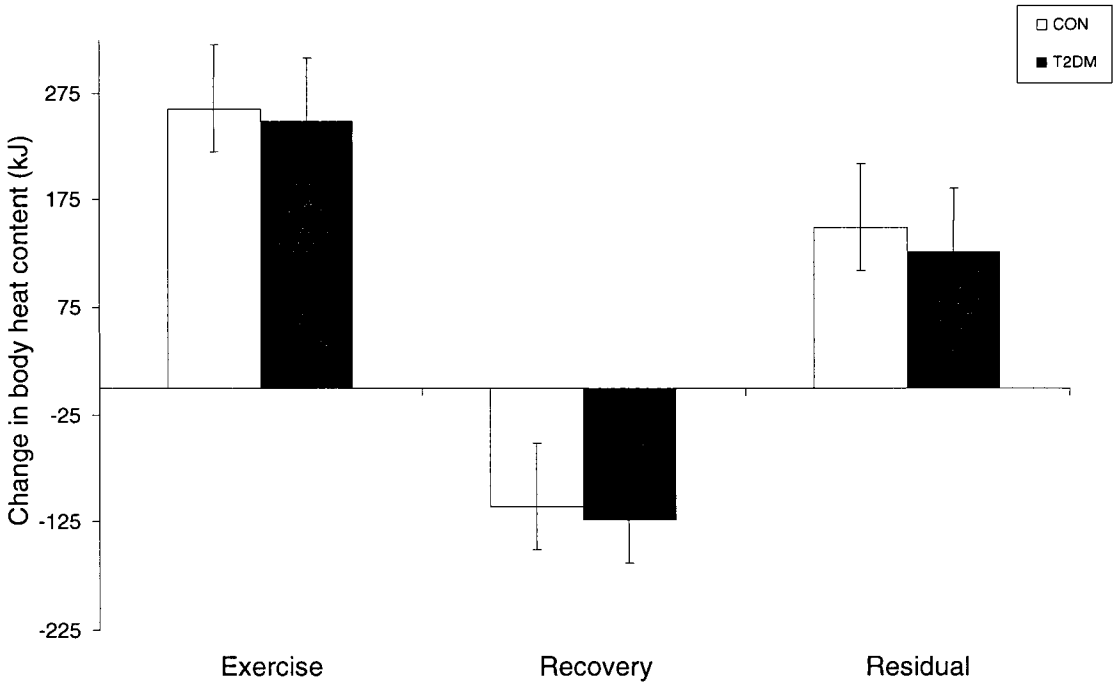

Figure 6. Changes in body heat content at 30°C. Values are group means presented as: total heat gained during exercise, total heat lost during recovery, and the residual heat stored by the end of the trial (ΔH_b from exercise minus ΔH_b from recovery). CON= control group; T2DM= type 2 diabetes group.

4.2 Core and skin temperatures

Temperate conditions (24°C)

At 24 °C, both the T2DM and CON groups had comparable responses. Both groups experienced a similar significant rise in rectal temperature from baseline to the end of the exercise period, (T2DM: +0.35 ± 0.12 °C, p=0.0004; CON +0.37 ± 0.14 °C, p=0.0006, but there were no differences between groups (p=0.79). This was followed by

a significant decline in rectal temperature in both groups from the end of the exercise period to the end of the recovery period [-0.43 ± 0.10 °C, in the T2DM group, p=0.0008; and -0.37 ± 0.17 °C in the control group, p=0.0017]; this change was not significantly different between groups (p=0.49). Both groups were able to resume baseline rectal temperature by the end of the one hour recovery period such that there were no significant differences between baseline and final rectal temperatures for the T2DM group, which started at 37.40 ± 0.2 C and ended at 37.32 ± 0.24, (difference of -0.08 ± .14 C, p=0.12) or the control group, which started at 37.06 ± 0.18 and ended at 37.06 ± 0.22, (difference of -0.00044 ± 0.13 p=0.50). There was no significant difference between groups for these changes from baseline to final rectal temperature, where p=0.35.

Hot conditions (30°C)

At 30°C, both groups had a similar rise (p=0.49) in rectal temperature from baseline to the end of the exercise period; the T2DM group rose 0.49 ±0.12 °C; p=0.0019, and the control group rose 0.59 ±0.26 °C; p=0.0033. This was followed by a significant decline in rectal temperature in both groups from the end of the exercise period to the end of the recovery period (-0.28 ± 0.14 °C in the T2DM group (p=0.014) and -0.36 ± 0.24 °C in the control group, (p=0.015); this change was not significantly different between groups (p=0.57). Both groups were unable to resume their baseline rectal temperature by the end of the one hour recovery period. The changes from baseline to the end of the trial were not significantly different between groups; p=0.80). The T2DM group had a mean rectal temperature of 37.49 ± 0.26 °C at the end of the trial, which was 0.21± 0.08 °C greater than at baseline 37.27 ± 0.21 °C (p=0.013). The control group had similar results, finishing the trial at 37.24 ± 0.26 °C, which was 0.18 ± 0.18)

°C higher than baseline (p=0.03).

Mean skin temperature values were not significantly different between groups during exercise or recovery in either condition, however there was a significant effect of time for all trials (p=0.05); (See Figure 7.)

4.3 Local heat loss responses

4.3.1 Skin blood flow

Absolute SkBF -measured in arbitrary perfusion units (PU)- showed no differences between groups at any time during the trials, despite a trend towards lower values in the T2DM group. However, during local forearm heating (performed after each trial), Max SkBF was found to be significantly diminished in the T2DM group with the T2DM group reaching only ~60% of the SkBF capacity that the control group reached. This happened during both trials as follows in T2DM and CON groups respectively: 66 ± 20 vs. 118 ± 55 PU, (p=0.045) at 24°C and 66 ± 35 vs. 104 ± 27 perfusion units, p=0.049 at 30°C – (See Figure 8).

Relative to Max SkBF, the T2DM group had significantly higher %SkBF values than the control group in the temperate and hot conditions (both p<0.0001). During the last 30 minutes of exercise, the T2DM group had an average %SkBF of 61 ± 0.03 % and 68 ± 0.04 % whereas the control group was at 45 ± 0.03 % and 51 ± 0.03 % in temperate and hot conditions respectively (See Table 2).

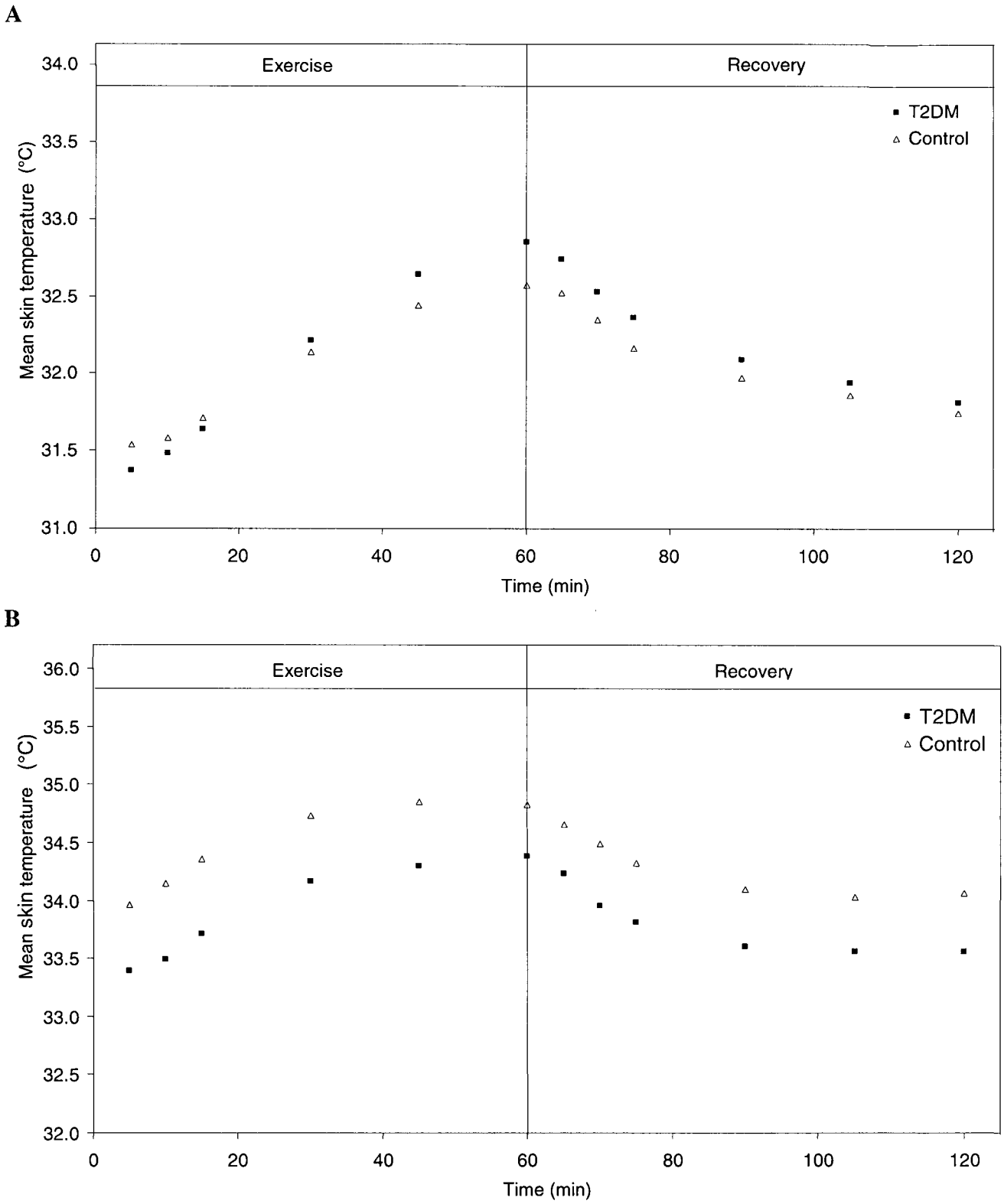

Figure 7. Mean skin temperatures (°C) at selected time intervals during exercise and recovery in 24°C (Panel A) and 30°C (Panel B) ambient conditions. T2DM= type 2 diabetes group; CON, control group.

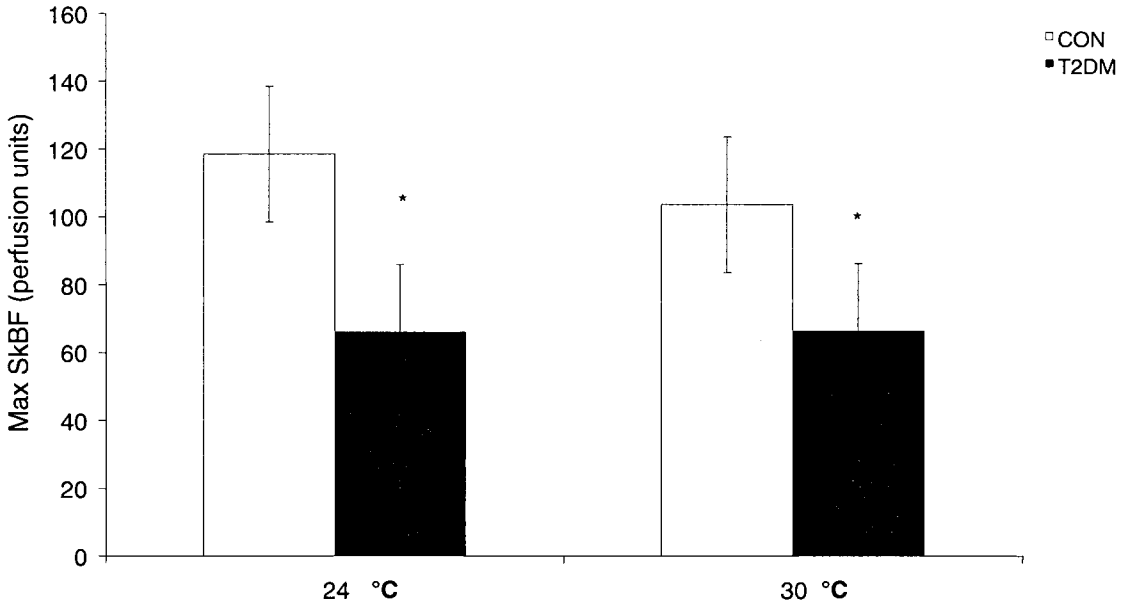

Figure 8. Mean Max SkBF response measured following recovery at 24 and 30°C. Values were significantly lower in the group with diabetes (T2DM) compared to a control group (CON) under both ambient conditions. * significantly different from control group ($p < 0.05$)

These trends continued into the recovery period with the T2DM group showing significantly higher %SkBF than the control group in both the temperate and hot conditions (both <0.0001). During the last 30 minutes of recovery, the T2DM group had an average %SkBF of 28 ± 0.02 % and 33 ± 0.02 % and the control group had an average of 18 ± 0.02 % and 22 ± 0.03 %.

4.3.2 Cutaneous vascular conductance

The mean %CVC followed similar trends as the %SkBF in the temperate condition, where the T2DM group had significantly higher values ($p<0.05$) than the control group at baseline, 10 minutes into exercise, and for the last 40 minutes of the recovery period, (See Table 5). Mean %CVC was not different between groups at any time before, during or after exercise in the hot condition, (See Table 6).

Table 2. Percent SkBF at baseline, during exercise, and during recovery

Measure	Group	Baseline	Exercise (min)						Post-Exercise (min)					
			10	20	30	40	50	60	10	20	30	40	50	60
24°C														
% SkBF	**T2DM**	29 (2.8)*	36 (1.4)*	41 (2.9)*	48 (2.7)*	55 (1.4)*	60 (2.8)*	60 (1.7)*	50 (3.0)*	37 (2.0)*	36 (1.8)*	25 (1.9)*	28 (1.6)*	28 (2.2)*
	Control	18 (1.7)	24 (1.4)	33 (2.3)	34 (2.0)	44 (1.0)	44 (1.7)	36 (2.2)	28 (1.8)	31 (2.2)	21 (2.1)	19 (1.5)	14 (1.6)	20.4 (2.2)
30°C														
% SkBF	**T2DM**	34 (1.9)*	52 (2.8)*	60 (0.9)*	60 (2.9)*	69 (2.2)*	69 (2.1)*	57 (1.1)*	53 (2.9)*	50 (2.1)*	38 (3.7)*	33 (2.1)*	34 (2.6)*	38 (2.2)*
	Control	25 (1.7)	39 (1.6)	44 (2.1)	46 (1.9)	46 (1.3)	55 (2.4)	42 (2.2)	30 (2.0)	30 (2.3)	26 (2.6)	25 (2.5)	20 (3.3)	29 (7.9)

* significantly different from control group ($p < 0.05$)

4.3.3 Local Sweating response

Sweat rates showed a trend ($0.05<p<0.09$) for greater sweating on the shoulder in the T2DM group during recovery at 24°C only (See Table 5). Overall, there was an effect of time ($p<0.001$) for both groups. In each group there was a sudden rise in humidity in the sweat capsule due to the onset of sweating, followed by a gradual rise and leveling off during exercise, ending with a slow return to resting conditions in the temperate trials, and a level slightly above resting conditions in the hot trials.

In the 30 °C condition, the T2DM group sweat less on the shoulder than the control group did, however this difference was not significant, (See Table 6).

4.3.4 Blood pressure and heart rate

Despite elevated values in the T2DM group compared to the CON group, there were no significant differences throughout all trials for systolic blood pressure (SBP), diastolic blood pressure (DBP) or mean arterial pressure (MAP). (See Table 5 and Table 6).

Heart rate (HR) varied significantly over time ($p<0.001$) for both groups. Overall, the T2DM group had higher values compared to the control group. These between group differences were significantly higher (by 10-20 bpm) in the T2DM group at baseline ($p<0.05$) and throughout exercise ($p<0.05$) in the temperate condition, whereas differences between groups only approached significance ($0.050 < p < 0.095$) during the last 40 minutes of exercise in the hot condition. (See Table 5 and Table 6).

During every point in the recovery period, in both the temperate and hot conditions, HR was significantly higher ($p<0.05$) in the T2DM group. (See Table 5 and Table 6).

5.4 Perception responses

4.4.1 Perceived exertion

Perceived exertion (PE) was measured on the Borg Scale, from 6-20. There was a significant effect of time for all subjects in all trials, which showed a gradual increase in PE between the onset and end of the exercise period (See Table 3). The average PE started at 8 and went up to 13 ± 2. There were no differences between groups in any trials.

Table 3. Perceived Exertion

		Exercise (min)				
	Group	**10**	**20**	**30**	**40**	**50**
24°C						
Borg - Perceived exertion (6-20)	T2DM	10 (3)	11 (2)	11 (2)	12 (2)	12 (2)
	Control	11 (1)	11 (1)	13 (2)	13 (2)	14 (3)
30°C						
Borg - Perceived exertion (6-20)	T2DM	10 (2)	11 (2)	11 (2)	12 (2)	13 (2)
	Control	11 (1)	12 (2)	12 (2)	13 (1)	13 (1)

4.4.2 Thermal sensation

Thermal sensation (a score from 0 to 7) during exercise ($p=0.017$) and recovery ($p=0.006$) was significantly different between the 24 and 30 degree trials. At both temperatures, there was also a significant effect of time over the entire trial, where $p<0.01$. The difference between groups came close to reaching significance ($p=0.058$) at the 50-minute mark during the exercise period, showing that the control group felt hotter (5/7) than the T2DM group (3/7) in the 30°C condition, but there were no such differences in the 24°C condition (See Tables 5 and 6). There were no significant differences between groups in the 24 or 30°C conditions during the recovery period, however, both temperature conditions exhibited a significant effect of time ($p<0.001$), which saw the TS gradually decline from the end of exercise to the end of the recovery period.

4.5 Blood glucose responses

Mean blood glucose was significantly higher in the T2DM group from baseline to the end of the trial in both the 24°C and 30°C conditions (See Table 4).

Table 4. Blood Glucose (mmol/L)

			Exercise (min)			Post-Exercise (min)		
	Group	**Baseline**	**10**	**30**	**50**	**10**	**30**	**50**
24°C Blood Glucose	T2DM	7.0 (0.9)*	6.6 (0.6)*	6.4 (1.2)*	5.7 (1.3)†	6.0 (1.2)†	6.3 (1.2)†	6.3 (0.9)*
	Control	5.3 (0.7)	5.0 (0.5)	4.8 (0.7)	4.9 (0.7)	5.1 (0.6)	5.3 (0.9)	5.1 (0.6)
30°C Blood Glucose	T2DM	7.9 (1.7)*	7.7 (1.6)*	7.1 (1.7)*	7.4 (1.7)*	7.1 (0.9)*	6.9 (0.7)*	6.9 (1.1)*
	Control	5.1 (0.7)	5.0 (0.6)	5.0 (0.7)	5.1 (0.6)	5.1 (0.8)	5.2 (0.5)	5.3 (0.8)

* - significantly different from control group ($p=< 0.05$); † - approaches significant difference from control group ($p = 0.051 - 0.095$)

Table 5. Mean changes in cardiovascular and thermal responses during and following exercise in 24°C

		Exercise (min)							Post-Exercise (min)					
	Group	Baseline	10	20	30	40	50	60	10	20	30	40	50	60
CVC (% of max)	T2DM	26 (8)*	45 (12)*	53 (13)	55 (15)	58 (22)	61 (28)	52 (25)	35 (15)†	29 (10)*	27 (11)*	28 (11)*	27 (11)*	27 (10)*
	Control	14 (6)	34 (16)	40 (23)	42 (24)	43 (25)	43 (25)	40 (24)	20 (13)	16(7)	15 (5)	13 (5)	14 (4)	14 (5)
SBP (mmHg)	T2DM	136 (13)	159 (19)	158 (19)	161 (16)	161 (14)	158 (11)	153 (13)	135 (11)	137 (14)	132 (16)	135 (13)	132 (13)	140 (20)
	Control	128 (8)	147 (11)	148 (11)	150 (11)	154 (14)	153 (15)	140 (12)	132 (9)	129 (8)	128 (7)	127 (4)	127 (5)	130 (5)
DBP(mmHg)	T2DM	79 (6)	82 (8)	83 (8)	83 (8)	81 (8)	82 (7)	84 (6)	80 (7)	81 (7)	81 (8)	81 (9)	82 (10)	83 (10)
	Control	79 (8)	82 (7)	82 (7)	82 (8)	82 (8)	83 (7)	82 (8)	82 (7)	81 (10)	81 (11)	83 (9)	84 (9)	83 (9)
MAP(mmHg)	T2DM	98 (10)	107 (10)	107 (11)	108 (10)	108 (10)	107 (7)	108 (6)	99 (7)	100 (8)	100 (9)	100 (7)	101 (10)	103 (13)
	Control	96 (6)	103 (6)	104 (5)	104 (9)	106 (7)	106 (8)	103 (5)	99 (5)	97 (8)	97 (7)	98 (6)	100 (6)	99 (7)
HR (bpm)	T2DM	86 (8)*	110(15)†	118(15)*	118(14)*	121(15)*	119(16)*	120(19)*	102(18)*	97(15)*	93(12)*	95 (13)*	94 (13)*	92 (12)*
	Control	71 (11)	97 (9)	99 (9)	100 (10)	101 (9)	100 (11)	99 (11)	80 (10)	77 (9)	73 (10)	78 (11)	74 (11)	74 (11)
LSR_{trap} ($mg/cm^2/min$)	T2DM	0.09(0.03)	0.16(0.03)	0.22(0.05)	0.31(0.07)	0.35(0.08)	0.37(0.09)	0.41(0.10)	0.23(0.08)†	0.21(0.08)†	0.21(0.09)*	0.22(0.08)†	0.21(0.10)†	0.20(0.10)†
	Control	0.15(0.11)	0.11(0.08)	0.15(0.15)	0.23(0.20)	0.24(0.21)	0.29(0.24)	0.28(0.23)	0.15(0.09)	0.11(0.09)	0.10 (0.08)	0.12(0.11)	0.11(0.09)	0.11(0.08)
Thermal sensation (0-7)	T2DM	1.0 (1.0)	1.7 (1.3)	2.1 (1.5)	2.4 (1.0)†	3.1 (0.9)	3.1 (0.9)	3.1 (0.9)	1.9 (0.7)	1.1 (0.7)	0.71 (0.5)	0.3 (0.5)	0.0 (0.6)	0.1 (0.7)
	Control	1.2 (1.2)	1.9 (1.7)	2.4 (1.5)	3.6 (1.1)	3.7 (1.1)	4.3 (1.5)	3.9 (1.7)	2.6 (1.8)	2.0 (2.5)	1.6 (2.6)	11.1 (2.3)	1.1(2.3)	11.1(2.7)

* - significantly different from control group (p=< 0.05); † - approaches significant difference from control group (p = 0.051 - 0.095)

Table 6. Mean changes in cardiovascular and thermal responses during and following exercise in 30°C

		Exercise (min)							Post-Exercise (min)					
	Group	Baseline	10	20	30	40	50	60	10	20	30	40	50	60
CVC (% of max)	T2DM	23 (9)	43 (10)	51 (15)	55 (15)	55 (16)	54 (15)	46 (15)	36 (15)	30 (10)	26 (8)	23 (8)	25 (8)	21 (16)
	Control	20 (12)	41 (19)	42 (18)	46 (19)	49 (18)	47 (20)	39 (14)	22 (14)	21 (14)	19 (11)	17 (7)	18 (8)	17 (8)
SBP (mmHg)	T2DM	143 (12)	169 (18)	168 (20)	167 (20)	166 (18)	165 (19)	159 (28)	135 (17)	133 (19)	135 (16)	132 (15)	130 (16)	131 (18)
	Control	134 (16)	153 (12)	153 (11)	154 (12)	154 (13)	156 (13)	148 (16)	135 (18)	136 (16)	137 (13)	136 (15)	133 (15)	133 (14)
DBP(mmHg)	T2DM	84 (9)	85 (11)	84 (10)	84 (8)	84 (8)	83 (8)	82 (9)	80 (9)	80 (12)	81 (13)	82 (11)	81 (11)	80 (10)
	Control	79 (13)	84 (12)	86(12)	85 (13)	84 (12)	85 (11)	82 (10)	83 (12)	83 (12)	82 (14)	83 (12)	85 (10)	84 (11)
MAP(mmHg)	T2DM	103 (14)	113 (12)	112 (12)	111 (11)	111 (11)	111 (11)	106 (17)	98 (10)	99 (12)	98 (13)	100 (11)	98 (11)	97 (9)
	Control	97 (11)	107 (11)	108 (12)	107 (11)	105 (12)	109 (11)	103 (11)	101 (12)	101 (11)	100 (12)	101 (12)	101 (10)	100 (10)
HR (bpm)	T2DM	88 (13)	108 (12)	118 (14)†	119 (15)†	121 (17)†	123 (16)†	125 (16)†	112 (23)*	104 (18)*	101 (18)*	99 (17)*	99 (17)*	98 (17)*
	Control	74 (9)	105 (15)	103 (13)	105 (13)	107 (12)	107 (11)	107 (11)	83 (13)	82 (10)	79 (9)	82 (10)	79 (10)	80 (9)
LSR_{trap} ($mg/cm^2/min$)	T2DM	0.15(0.08)	0.22(0.08)	0.33(0.10)	0.37(0.09)	0.37(0.07)	0.43(0.12)	0.43(0.11)	0.32(0.11)	0.23(0.10)	0.23(0.09)	0.21(0.11)	0.22(0.12)	0.19(0.14)
	Control	0.19(0.11)	0.30(0.13)	0.37(0.21)	0.42(0.21)	0.44(0.22)	0.47(0.22)	0.45(0.25)	0.30(0.13)	0.26(0.11)	0.24(0.10)	0.22(0.10)	0.21(0.11)	0.19(0.11)
Thermal sensation (0-7)	T2DM	2.0 (0.8)	2.4 (0.9)	2.7 (1.1)	3.0 (1.3)	3.4 (1.3)	3.4 (1.4)†	3.6 (1.6)	2.0 (1.3)	1.4(1.0)	1.4 (1.0)	1.3 (1.0)	1.0 (1.2)	0.9 (0.9)
	Control	2.0 (1.5)	3.3 (1.3)	3.6 (1.4)	4.1 (1.2)	4.3 (1.4)	5.0 (1.4)	4.9 (1.6)	3.7(2.6)	3.1 (2.2)	2.9 (2.3)	2.4 (2.0)	2.1 (2.0)	2.0 (2.2)

* - significantly different from control group (p=< 0.05); † - approaches significant difference from control group (p = 0.051 - 0.095)

CHAPTER V

Discussion

The present study was designed to investigate the differences in whole body heat storage between individuals with and without type 2 diabetes mellitus during and after moderate intensity cycling exercise performed in temperate (24°C) and hot (30°C) ambient conditions. Contrary to our hypothesis, the T2DM group did not exhibit any reduction in whole body heat loss capacity compared to controls. The T2DM group actually lost a greater proportion of heat compared to what the control group did, but this difference was only significantly different in the temperate condition (See Figure 3).

Previous studies suggest that individuals with T2DM have a reduced capacity for whole body heat loss compared to individuals without this disease. Our results are contrary to these suggestions, as calorimetry data indicate that the T2DM group was able to dissipate heat in a similar capacity to the CON group. Furthermore, there were no significant differences in whole body heat loss during exercise or recovery, nor were there differences in the components of heat loss (dry and evaporative) between groups. This is contrary to our hypothesis that the T2DM group would exhibit reduced heat loss capacities. We did not observe any reductions in local sweating or SkBF between groups as previous studies have reported (Gibbons, 2009; Petrofsky et al., 2005b).

These results reinforce findings which indicate that changes in local heat loss mechanisms do not necessarily reflect changes in whole body heat loss. This finding may be due to a compensatory effect by the T2DM group, as they were shown to be at a higher percentage of their maximum skin vasodilation capacity compared to the control group throughout exercise and recovery in all trials.

Such a finding brings up a serious limitation in past research: Because previous studies used only *absolute* SkBF values to make assumptions about heat loss instead of *relative* SkBF values, they did not likely take into consideration the possibility that one individual may function at a greater percentage of their capabilities despite lower absolute values. This appears to be exactly what happened in this study. The absolute SkBF in the T2DM group was not significantly different from the control group but when compared as a % of Max SkBF, differences were significant. The intriguing thing about this observation is that none of these differences interfered with whole body heat loss, which begs to question the effectiveness of measuring local SkBF by a single laser Doppler, regardless of using absolute or relative values. The Doppler can only measure flow under a microscopic area, and that one area may be ridden with nerve damage, or it may be a very responsive to the slightest change in temperature. Presently, the best way to compare SkBF by is relative values, yet these readings do not represent a clear picture of the whole limb or whole-body response to any stimulus. In this study, the T2DM group actually worked at a higher percentage of their Max SkBF during exercise compared to the control group, which may be an example of the body's ability to compensate for undiagnosed cardiovascular and nervous system discrepancies.

5.1 Calorimetry responses

As previously mentioned, there were no differences between groups for heat gain and loss during exercise and recovery. However, residual heat storage was less in the T2DM group compared to the CON group in both conditions, reaching a significant difference at 24°C ($p=0.042$), and showing a trend towards being significantly lower at

30°C. Though it is unclear as to why the T2DM group lost a greater percentage of heat than the CON group, what is clear, is that this particular group of individuals with T2DM are not suffering from any type of thermoregulatory impairments. The slightly higher VO_{2max} (aerobic fitness) in the T2DM group may be responsible for this greater heat loss, however, correlation analysis did not yield any significance for this comparison ($p>0.1$)

5.2 Thermal responses

No relative group differences occurred for T_{rec} between baseline and end-exercise, or between baseline and end-recovery. This suggests that the T2DM group gained and lost body heat in a similar way that the CON group did. However, the T2DM group began with and maintained significantly higher absolute T_{rec} values than the CON group, though it is unclear as to why this difference persisted. Some studies suggest that individuals with T2DM have an elevated metabolic rate (Ohtsuka et al., 1995) and also that they are more likely to oxidize fat (Boon *et al.*, 2007) than non-diabetic individuals, which would account for the greater heat in the body to begin with. However, there an equal amount of studies which provide information to directly oppose these claims (Gaster, 2009; Mogensen *et al.*, 2009). So the next influence most likely to affect core body temperature is the specific heat capacity of the body, which is based on body composition. But since our groups were matched for body fat percentage, then we must consider the possibility that the fat distribution and muscle mass differences could have contributed to the higher absolute mean rectal temperatures. However, upon further analysis, there were no differences between groups for the interaction of heat loss and body fat distribution ($p>0.09$), nor was there a difference between groups for any

measure of body heat loss as a function of muscle mass (kJ of heat loss/gain per kg of fat free mass), ($p>0.09$).

5.3 Hemodynamic responses

While all T2DM participants who were hypertensive took their medication as normal, it appears as if there was still a discrepancy between their response and that of the control group, who did not have high blood pressure. Findings of an exaggerated HR and BP at rest and during exercise were noted in previous studies in participants with T2DM compared to a control group.

Unexpected findings in this study included higher heart rate, and %CVC in the T2DM group at various points throughout both trials. The higher heart rate may be related to the vascular status of the T2DM group, as all but one of the individuals in this group was taking anti-hypertensive medications, whereas no one in the control group took any medications. The higher %CVC can be explained by looking at the components used to derive this value, where CVC = SkBF / MAP and %CVC is calculated from Max SkBF / MAP during the Max SkBF measurement which takes place over a five-minute period. When CVC is reported as an absolute value, (similar to VO_2 in L/min), it does not enable comparison between individuals, so it was represented here, and in other studies (Carter et al., 2002; W. S. Journeay et al., 2004; Wick et al., 2006), as a %CVC, using the individual's Max SkBF and MAP (calculated from blood pressure) to derive a value. Thus, the results of a higher %CVC for the T2DM group can be attributed to their lower absolute Max SkBF.

This study has provided evidence of reduced SkBF in response to local heating in individuals with T2DM, similar to other works (Petrofsky et al., 2008; Stansberry et al.,

1999). However, an interesting finding from this research is that during and following exercise, the T2DM group did have lower (though not significant) absolute SkBF values, but in terms of a percentage of Max SkBF, the T2DM group kept a consistently higher level of blood flow compared to the control group. Despite these differences in vascular capacity, there were no significant differences in whole body heat loss between individuals with and without T2DM. Recent work from our laboratory (using a protocol and ambient conditions similar to ours), demonstrated a lack of synchronization between local and whole body heat loss responses in young, healthy individuals which lends support to the notion that local heat loss responses are not representative of whole- body heat loss responses (G. P. Kenny et al., 2009).

5.4 Sweating responses

Changes in local sweating did not occur in parallel with whole body sweating in either group, lending support to previous studies which identified the strong influence of local skin temperature on sweat rate control.

These findings suggest that individuals with T2DM are able to compensate for the attenuations in local heat loss mechanisms by altering the whole body's response to heat stress.

5.5 Delimitations

Many studies involving individuals with type 2 diabetes matched their participants with a control group of similar age, height and weight; However these factors do not take into consideration the major physiological determinants of heat loss

capacity (Havenith, 1995) Factors such as body composition, body surface area, and maximal oxygen consumption (VO_{2max}) are much more directly involved with one's capacity to create and dissipate heat (Havenith & van Middendorp, 1990). So, in order to maintain the same level of comparisons as previous studies, we matched our participants by age, height and weight; but more importantly, we matched participants for VO_{2max} (ml/kg/min), body surface area (BSA), body surface area-to-mass-ratio, and body composition (% fat). By matching participants for these additional elements, we have reduced the physical variability between our T2DM group and the control group which enables us to suggest that any differences between groups which arise in response to our protocol are likely due to diabetes and not some other factor.

Choosing individuals who were non-heat acclimated and unaccustomed to regular intense, exercise decreased inter-individual variability. These selection criteria were set to control for factors such as: onset of sweating, effectiveness of sweating, and maintenance of core temperature, all of which are affected by heat acclimation or acclimatization (Havenith & Middendorp, 1990). Matching for body surface area:mass ratio was done so as to ensure that all participants had the same potential for dry heat loss. In order to account for one's capacity to store heat, which is based on the specific heat of the tissues, we limited the amount of % body fat in our participants to 30-55% in females and 30-45% in males.

The point of using such exclusive criteria was to avoid the possibilities of impaired thermoregulation such as reduced skin blood flow and sweating that have been shown to be present in individuals with neuropathy or nerve damage. For the health and safety of our participants, we did not allow individuals to participate if they had foot

ulcers or loss of sensation in their feet or hands. Due to the increases in peripheral and arterial blood pressure during a maximal exercise stress test, we did not allow individuals with cardiac or retinal disease, or uncontrolled hypertension to participate in this study. Subjects were restricted from eating 2-hours prior to the start of testing. They were permitted water prior to the start of the test. For someone with no metabolic disorders, this period of time without food would not be a problem; however, for individuals who require insulin or for those with poor glucose control, the likelihood of experiencing a hypoglycemic episode is elevated. Some studies suggest that there may be an increased insulin uptake during and after exercise in the heat (Derouich & Boutayeb, 2002) which requires changes in carbohydrate ingestion or insulin dosage; Therefore, individuals taking insulin or who had poor glucose control (as represented by Hb_{A1c} of 10% or greater) were not permitted to participate due to the likelihood that they would not be able to maintain safe levels of blood glucose control throughout the experimental trials.

A primary goal of this study was to mimic real life situations as much as possible by:

1) using environmental conditions which are common in Canada, such as ambient temperatures of 24 and 30°C, and relative humidity between 10-50%;

2) choosing an exercise protocol (one hour long) that is representative of what the average person in this population may encounter during working conditions and leisure activities both indoors and outdoors – Ideally, we felt that a 30-minute exercise protocol would be more appropriate for this population, however, it was necessary to use a protocol of one hour to realize steady state values of metabolic heat production;

3) allowing subjects to have a meal and take all medications as normal before the exercise sessions. Many other studies make subjects go through a fasting period prior to

testing whereby they stop taking medications and avoid eating, which is not ideal for maintaining glucose levels during and after physical activity. In our situation, having a participant in an enclosed area without eating or taking the appropriate medications would have been dangerous and participants would likely have become hypoglycemic.

In order to minimize the effects of previous exercise on metabolism, body temperature, and the cardiovascular system, subjects were not permitted to do any vigorous or moderate activity 12 hours prior to the study and were also encouraged to avoid any hot environments before testing.

We purposely chose participants with T2DM who had levels of glycosylated haemoglobin (Hb_{A1c}) that were less than 10%, and a control group which had values less than 6% (as taken after a 12-hour fast) in order to ensure a significant difference in health status between groups. It was also important that our participants had no history or signs of distal neuropathy, and no past diagnosis of autonomic neuropathy (as screened by monofilament testing in our lab and by their doctor in the last year). Previous studies have shown that when participants with T2DM were classified separately (nerve damage vs. no nerve damage), only those with nerve damage showed significantly attenuated SkBF and sweating, which suggests that nerve damage is the cause of these local changes, and not T2DM. Currently, there is no research that has investigated whole body heat loss during and after exercise in the heat in older adults with T2DM who are free of clinically diagnosed nerve damage. The present study only allowed subjects to participate if told by their doctor in the last year that they do NOT have autonomic neuropathy or any other forms of nerve damage (eyes, feet). Participants were also subject to monofilament testing (feet) to rule out local nerve damage. This precaution was

taken to ensure that clinically diagnosed nerve damage would not influence our results. We matched subjects for fitness (VO_{2max} mL/kg/min), body fat %, BSA, height, weight, and age to control for metabolic and body surface area influences. We also had all subjects work at the same relative workload (ranging from 52-58% of their VO_{2max}), which ended up being very close in absolute workloads as well (~330 W workload).

By matching participants in each group for VO_{2max} (in ml/kg/min), this study has an advantage where previous studies were limited in their interpretation of results. This type of matching was necessary for this study because it is known that individuals with similar oxidative capacities are likely to have similar abilities to adapt to heat stress.

5.6 Limitations

These findings are limited in terms of their statistical power due to the small number of participants tested. Results must be interpreted with caution due to the specifications used in the selection criteria, which are not necessarily representative of the typical T2DM population.

In hindsight, another limitation to this study was the unexpected influence of air flow on convective heat loss during trials conducted in the temperate condition. Air flow throughout the chamber was kept constant and high in all trials so as to allow for effective evaporation of sweat from the skin. However, this appears to have created an increase in convective heat loss and may have attributed to the decreased core temperatures by the end of the trials in the temperate condition. On the other hand the air flow had to be kept at one constant level to enable effective evaporation of sweat in the hot condition.

CHAPTER VI

Conclusion

The current study was developed to confirm the findings of reduced skin blood flow and sweating, while at the same time, determining if there was a change in body heat storage that makes individuals with T2DM more susceptible to heat illness or injury. This was done through direct and indirect calorimetry, ensuring constant exercise while comparing the different reactions of healthy and diabetic subjects in a thermoneutral environment (24°C) and a hot environment (30°C). This study aimed at discerning whether or not these local changes amount to whole body changes in terms of thermoregulation. The results suggest that individuals with T2DM can thermoregulate adequately and similarly to matched non-diabetic individuals despite having a reduced Max SkBF. Overall, these findings suggests that previous reports of local reductions in sweating and skin blood flow in T2DM were likely limited to certain areas of the body, and do not significantly interfere with whole body heat loss.

Any findings which were different in the T2DM group are likely to be exacerbated in more intense heat stress situations, such as higher intensities of exercise, higher ambient temperatures, and higher humidity. It is also important to note that the responses of our participants with T2DM will not translate directly to others with the disease, especially those who are older, who may have lower aerobic fitness levels, and have co-morbidities. For these reasons, precautions must be taken by individuals with T2DM who attempt any lifestyle interventions, especially those which combine heat exposure and intense or prolonged exercise. Further research must be done to identify the risks associated with performing physical activity in the heat and thereby aid in the

creation of practical safety guidelines for individuals with T2DM who work or exercise under similar conditions.

CHAPTER VII

Future Considerations

Until more research is completed, it is essential to focus on preventing and delaying the onset of co-morbidities associated with diabetes. The number of people in Canada and the U.S. that are diagnosed with T2DM has increased each year, and is developing hand in hand with obesity, as the next pandemic health problem (Ford & Mokdad, 2008; Mo et al., 2006). Recently, it has been estimated that there are approximately two million Canadians living with Diabetes Mellitus, where 90% of these cases are diagnosed as Type 2 (Mo et al., 2006). The majority of literature on T2DM strongly suggests that this disease is more influenced by lifestyle than genetics, as is the case in the development of Type 1 Diabetes Mellitus. People living with T2DM often suffer from co-morbidities of the disease due to insulin resistance, chronic hyperglycemia and hyperinsulinemia. These co-morbidities often manifest in the form of obesity, hypertension, high cholesterol, retinopathy, nephropathy and peripheral neuropathy. Each of these complications -as well as the natural deterioration of the body with age- combine to impair the body's ability to function optimally. However, to the best of our knowledge, no study has examined the cumulative effects of these impairments on thermoregulatory control during heat exposure during and after exercise.

Though exercise is not as widely prescribed as medication, it is now encouraged by the Canadian Diabetes Association as a compliment to traditional diabetes management strategies. Changes in exercise and diet habits have proven to be effective in controlling blood glucose, reducing the deleterious effects of aging, and improving overall health-related quality of life. It is therefore essential that lifestyle modifications

are adopted by those who have T2DM or those who are at risk for developing this disease. Many researchers have even produced studies showing that exercise training can help to reverse the damaging effects of hyperglycemia, especially in terms of increasing insulin sensitivity and improving endothelial function in individuals with T2DM (Hamdy *et al.*, 2003; Sigal et al., 2007). Some more recent studies even suggest that weekly heat treatment, much like intense exercise, can improve glucose tolerance and prevent skeletal muscle insulin resistance (Gupte *et al.*, 2009). Before individuals with T2DM begin any exercise program, it is essential to note that many of the physical activities which are deemed safe in a healthy population can pose considerable health risks to those with T2DM (especially, those who also have hypertension, cardiovascular disease, nerve damage of the extremities, or those over 60 years old). These risks include: increased chance of myocardial infarction, stroke, foot ulcers, hypoglycemia, and various heat-related illnesses and injuries. Aside from difficulties controlling blood glucose levels during and after exercise, individuals with T2DM must pay special attention not to overheat or injure themselves when exercising in the heat or when performing endurance activities. This is due to the fact that many individuals with diabetes can develop impaired sensitivity to hot, cold, and pressure stimuli especially in their feet and hands. Caution must also be exercised because insulin has been shown to up-regulate during physical activity or heat exposure, and can increase a hypoglycemic episode. The 2008 Clinical practice guidelines recommend that any new exercise program for individuals with T2DM should be progressive and that glucose should be monitored carefully when making any changes to activity or nutritional habits to ensure a safe transition into a new lifestyle.

Significance

Through the findings from this research study, it is our intent to provide health care practitioners, industry standards policy makers, and human resource managers with a starting point to begin to understand the physiological similarities and differences between healthy individuals and those with T2DM when exposed to exercise and hot environments. Future research must now develop more challenging heat stress situations to discern where the threshold is for individuals with T2DM in terms of when they become unable to thermoregulate effectively. This type of knowledge has the potential to provide practical resources to practitioners and improve workplace and exercise safety through the development of standards that address the specific needs of individuals who are afflicted by T2DM and its varying degrees of complications.

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Appendix A
Telephone protocol for contacting former D.A.R.E. patients

Telephone protocol for contacting participants from the DARE study. For use in study: "Effect of type 2 diabetes on body heat storage during physical work."

Sample script:

Section A

INVESTIGATOR OR DELEGATE:

Hello, this is _____ calling on behalf of Drs. Ron Sigal and Glen Kenny. Previously, you participated in the Diabetes Aerobic and Resistance Exercise Study.

#1: Is this correct?

DARE participant: Yes/No

#1 response → if no, confirm the name and phone number on the list is incorrect;

INVESTIGATOR OR DELEGATE:

#1, a) clarification questions:
i) So, your name is not _____ _____?
ii) Does this person reside at this number, ###-####? –
if NO, then:

INVESTIGATOR OR DELEGATE:

Please excuse this intrusion; there must be a mistake on my list. Thank you for you day, and take care.

→ if yes, confirm full name.

INVESTIGATOR OR DELEGATE:

#2: Great. Do you have a few minutes to hear about a new study that is being conducted by the same investigators as the DARE study?

If Yes:	If No:
Proceed to section B	Ask appropriate clarification questions
If yes to clarification questions, go to section A2	If no to clarification questions, go to section A1

Clarification questions:

i) Is there a better time you can be reached at?

ii) do you wish to be contacted in the future regarding other research studies?

iii) what time is best for me to call you back?

Section A1

INVESTIGATOR OR DELEGATE:

Thank you for your time, I will remove your name and number from future contact lists.

Section A2

Possible responses to affirmative clarification questions:

Thank you, I will keep your name and number on our list for future contact purposes.

Confirm call-back time and say, "Ok, thank you, I will call you back then. Have a good day."

Section B:

INVESTIGATOR OR DELEGATE:

Thank you. I'm a researcher working with Dr. Glen Kenny and Dr. Ron Sigal, and currently, we're recruiting participants for an exercise study. We are hoping that you would consider participating in this new study. May I tell you a little bit about this new research study?

If Yes:	If No:
proceed to read study description.	them if they are interested in participating or coming into the lab to take a tour and get some more information
	If no to above question: thank them for their time and wish them well.

Study description.

We know that exercise is effective at improving blood sugars and many other factors which affect the quality of life for people who have diabetes, however there are other consequences of exercise which need to be explored. For example, when you exercise, you create and store heat in your body. At the same time, your body also works hard to get rid of the heat that is being created in order to maintain a balance between heat in and heat out. Recent findings have suggested that this balance doesn't work the same in

people who have type 2 diabetes. Specifically, there is a growing body of evidence that suggests that people with type 2 diabetes cannot sweat enough or make the necessary changes in their blood flow to help rid their body of the heat created during exercise. Since sweating and blood flow changes are what help get rid of heat in healthy individuals, and these heat-loss mechanisms may not function the same way in people with type 2 diabetes, we would like to measure changes in your heat loss during exercise. By directly measuring changes in your body heat, we will be able to see if the reduced sweating and blood flow reductions do in fact occur and if they prevent you from losing body heat at the same rate as a non-diabetic individual. To do this you would come to our laboratory at the University of Ottawa where you would perform exercise on a bicycle inside our temperature-controlled chamber so we can measure the changes in heat balance.

#3. Can I ask you a few questions about your health and history in order to see if you qualify for this study?

If Yes:	If No:
Brief them on what the study is about and what their participation would include.	Ask: Would you prefer that I send you a list of specific criteria by mail or email?
begin asking the criteria on the poster	Proceed to end phone call by gaining contact information and permission to send out poster.

Criterion on the poster:
-are you between 35 and 55 years old?
-do you smoke? Or are you exposed to second hand smoke on a regular basis?
-have you been diagnosed with diabetes for at least 5 years but no more than 10?
-have you developed any new medical conditions that would limit your ability to exercise?
-do you have health problems that prevent you from strenuous exercise?
-have you ever been told by a doctor or other health care professional that you should not participate in strenuous exercise?
-when was your last eye exam? Did the eye doctor apply drops to your eyes in order to look at the retina (back of the eye)? Were any problems found?
-Do you have any numbness, tingling or pain in your toes?
-Have you ever had heart problems, stroke, or unusual difficulty breathing?
-have you gained or lost body weight in the last 3 months? (Change of <5% of body weight, no more than 2-4 kg or 4-10 lbs)
-have you stopped or started taking any medications in the last 2 months?
-are you aware of any recent dose changes in medications that you are currently taking?
-do you have your blood sugar under control? If so, how do you control it? (by using exercise, diet, medications or any combination of these)
-do you take insulin?

- are you taking any inhalers of any kind?
-do you have any joint problems in your hips, knees, lower back, or ankles which would prevent you from exercising on a bicycle? (identify where and what severity injury is – also how recent. Ask if they have had surgery on any of those joints in the last year.

INVESTIGATOR OR DELEGATE:

#4. Do you have any questions or concerns at this point or can I continue with a description of the time and locations used for this study?

The study will be conducted over 1 – 2 weeks, depending on when you are available to come in. If your are selected for the study, you will be required to attend a pre-screening session, 2 experimental trial sessions at The University of Ottawa's Human Bioenergetics and Environmental Physiology Laboratory, and 2 diagnostic screenings; one at the University of Ottawa Clinic, and the other at Montfort Hospital.

#5. Does this study interest you?

If Yes:	If No:
When would you have time to come in to the Laboratory at the University of Ottawa to take a tour and receive an information package?	Thank you for your time. Have a good day.
Schedule appointment as applicable.	

Appendix B
Ethical Approval

Université d'Ottawa University of Ottawa

HEALTH SCIENCES AND SCIENCE RESEARCH ETHICS BOARD

CERTIFICATE OF ETHICAL APPROVAL

This is to certify that the University of Ottawa Health Sciences and Science Research Ethics Board has examined the application for ethical approval of the research project entitled **Effects of Type 2 Diabetes on Body Heat Storage During Physical Work (file H 03-07-04)** submitted by Glen Kenny from the School of Human Kinetics and Ronald Sigal from the Department of Medicine of the University of Calgary. Also participating in this research is Candice Brown a Master's student from the School of Human Kinetics of the University of Ottawa. The Board found that this research project met appropriate ethical standards as outlined in the Tri-Council Policy Statement and in the Procedures of the University of Ottawa Research Ethics Boards, and accordingly gave it a Category 1a (approval). This certification is valid one year from the date indicated below.

Rita D'Alessandro
Protocol Officer for Ethics in Research
For Dr. Daniel Lagarec, Chair of the
Health Sciences and Science REB

May 1, 2007
Date

Université d'Ottawa | University of Ottawa

October 17, 2008

Glen Kenny
School of Human Kinetics
Faculty of Health Sciences

Candice Brown
School of Human Kinetics
Faculty of Health Sciences

Object: **Effects of Type 2 Diabetes on Body Heat Storage during Physical Work (file H 03-07-04)**

Dear Dr. Kenny and Ms. Brown,

The Health Sciences and Science Research Ethics Board has examined your request received on June 24, 2008 for ethics approval of the following modifications to the above-mentioned project:

- Researchers would like to modify their screening criteria in order to include participants who have a history of cardiovascular problems at the condition that:

a) they have received medical clearance from their doctor to participate in exercise;
b) it has been at least six months since any major cardiac event or surgery;
c) they have had no problems or changes to cardiovascular health status in the last 6 months.

- Researcher would like to change their participant screening profile to include any diabetic participants who have had diabetes for at least 5 years instead of 10 years.
- Mathematical signs will be removed from the consent form and researchers will clarify the requirements for glucose control using positive wording only.
- Researchers would like to use the DEXA method for analyzing body composition as an alternate to the hydrostatic weighing method due to recent damages to the hydrostatic weighing apparatus. The radiation from the DEXA is approximately one tenth of a normal x-ray.
- Since participants can be 65 years old, researchers do not require that women still have a menstrual period. Women of this age will participate if they have been menopausal for one year (no menses at all).

Your request has been accepted. The certificate of ethical approval granted on May 1st, 2007 and valid until May 1st, 2009 covers these modifications.

During the course of the study, any further modifications to the protocol or forms may not be initiated without prior written approval from the REB. You must also promptly notify the REB of any adverse events that may occur.

If you have any questions, please do not hesitate to contact me at 613-562-5841.

Sincerely yours,

Germain Zongo
Protocol Officer for Ethics in Research
For Daniel Lagarec, Chair of the Health Sciences and Sciences REB