Understanding the effects of type 2 diabetes on heat dissipation during heat stress

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Thesis submitted to the
Faculty of Graduate and Postdoctoral Studies
In partial fulfillment of the requirements
For the degree of Doctor of Philosophy – Human Kinetics

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THESIS ABSTRACT

This thesis examined the extent to which type 2 diabetes (T2D) affects the body’s ability to dissipate heat during passive and exercise heat stress. Three experimental studies were performed to examine 1) whole-body heat loss and heat storage in habitually active older adults with and without T2D during a 3-hour resting exposure to extreme heat, 2) local and whole-body heat loss responses between older habitually active males with and without T2D during exercise at increasing fixed exercise intensities (and therefore level of heat stress) in the heat, and 3) whether short-term heat acclimation could reduce T2D-mediated impairments in whole-body heat dissipation. The first study showed that older adults with T2D did not have impaired whole-body heat loss (T2D: 75±25 W; Control: 71±22 W, P=0.90) and heat storage (T2D: 344±111 kJ; Control 346±139 W, P=0.98) and thus experienced similar thermal strain compared to their healthy counterparts during a 3-hour passive extreme heat exposure. The second study showed that T2D impaired whole-body evaporative heat loss in a heat load-dependent manner, such that a lower response was observed during moderate (211±26 vs. 229±23 W m⁻², P=0.04) and high (234±36 vs. 261±30 W m⁻², P=0.03), but not low (172±23 vs. 184±17 W m⁻², P=0.12), intensity exercise in hot, dry conditions. This led to the T2D group storing progressively more heat with each successive exercise bout relative to their healthy counterparts, leading to a 27% greater change in body heat storage for T2D (651±204 kJ) compared to Control (476±157 kJ, P=0.01) over the three exercise bouts. In the third study, short-term heat acclimation increased evaporative heat loss by as much as 13±5% for T2D, whereas it was only increased by as much as 6±6% for Control (P=0.01). As a result, evaporative heat loss was similar between groups during moderate (239±25 vs. 254±16 W m⁻², P=0.15) and high (T2D: 279±27; Control: 294±19 W m⁻², P=0.21) intensity exercise following heat
acclimation, leading to similar body heat storage between groups (T2D: 380±172 kJ; Control: 297±116 kJ, P=0.14). Altogether, the results of this thesis showed that habitually active older adults with well-controlled T2D do not display an impaired capacity to dissipate heat during passive heat exposure, albeit impairments in heat dissipation became evident at exercise-induced heat loads ≥200 W·m⁻² when performed in dry heat, with the magnitude of that impairment becoming greater with increases in heat load. These impairments in evaporative heat loss capacity can be mitigated by short-term heat acclimation and possibly reduce the risk of heat-related illness during exercise and/or work in the heat.
ACKNOWLEDGEMENTS

I would like to take this opportunity to sincerely thank those who have made this thesis possible and to the following individuals for their unconditional support and guidance throughout the various stages of my degree.

First and foremost, I would like to thank my supervisor, Dr. Glen Kenny, for giving me the opportunity to pursue my graduate studies in his laboratory. Over the past eight years, you have supported and challenged me to be better and to overcome all obstacles along the way. The passion and commitment that you have towards your research program and your graduate students is unparalleled. It has been a privilege to have had the opportunity to learn from you.

To my committee members Dr. Heather Wright Beatty, Dr. Ronald Sigal, Dr. Michael De Lisio, and Dr. Dominique Gagnon: Thank you for your time and effort in providing me with additional guidance and your feedback throughout this process has been excellent.

To my fellow past and present HEPRU colleagues: Thank you for your continuous encouragement and support throughout these years. Thank you to all the individuals who willingly gave up their time to participate in these experiments. Your contribution to science was invaluable.

To Dr. Sean Notley, thank you for your continuous support, guidance and feedback during the final months of data collection and throughout the writing process. You were instrumental to the success of this thesis.

I would like to thank my mother, Lyne and my father, Pierre. You have always been there to support me, and it is because of you that I continue to persevere towards my ambitions and goals.

I would like to particularly thank my wife, Stéphanie. Your everlasting support, encouragement, understanding and optimism have made me persevere to complete this chapter in our lives.

Finally, I would like to thank my extended family and friends for their encouragement while completing this degree. I would like to extend a special thank you to my parent in-laws, Danielle and Michel. It’s almost as though you both have a sixth sense as to knowing when I needed that extra push and motivation. Thank you for being there for me and your daughter throughout the ups and downs that we both encountered along the way.
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CHAPTER 1

INTRODUCTION
1.1. Introduction

Aging is associated with a progressive decrease in the body’s physiological capacity to dissipate heat and, therefore, maintain a safe and stable core temperature during extreme heat events and/or physical activity in the heat (1-7). This has been attributed to attenuations in the heat loss responses of sweating and skin blood flow. The former is thought to be the result of decreases in cholinergic sensitivity (8-10) as well as structural changes to the sweat gland itself resulting in reductions in sweat gland output (11). The latter has been associated to cardiovascular changes (i.e., reduced cardiac output and less redistribution of blood from the splanchnic and renal vascular beds) (12), structural alterations and/or a reduction in the number of cutaneous blood vessels (13), as well as a lower thermosensitivity of the response (14). This attenuated increase in skin blood flow has also been linked to a decrease in nitric oxide bioavailability (15-18), which has recently been shown to also contribute to a lower sweating response in older adults (19).

The local impairments in heat dissipation have been shown to translate into reduced whole-body heat loss and thus greater body heat storage in older relative to younger adults during heat stress (1-7). First, Stapleton et al. (5) demonstrated that habitually (i.e., ≥3 days per week of continuous exercise of 30–60 min per session) active older adults (~65 years) stored 1.6 and 1.3-times more heat during a 2-hour passive heat exposure in a hot-dry (36.5°C and 20% relative humidity) and hot-humid (36.5°C and 60% relative humidity) environment, respectively, compared to young (~21 years) healthy adults. While the rate of evaporative heat loss was similar between age groups in both conditions, the older adults had a greater rate of dry heat gain (heat gained from the environment under the conditions tested) of ~5 W m⁻² throughout both exposures, leading to the greater body heat storage. In a follow-up study, Kenny et al. (1) demonstrated that habitually active older adults (~62
years) stored 1.8-times more heat in their bodies than their younger (~23 years) counterparts during a 3-hour passive exposure in a more extreme heat condition (44°C). This was the result of an attenuated increase in evaporative heat loss during the initial 30 minutes after which the older adults were unable to compensate for a ~6 W·m⁻² greater dry heat gain throughout the remainder of the exposure.

Age-related impairments in the body’s ability to dissipate heat occur as early as 40 years of age during exercise in the heat (2). Specifically, it was recently reported that whole-body heat loss was reduced in older males and females during intermittent exercise (4 bouts of 15-min exercise at a metabolic heat load of 200 W·m⁻² for males and 175 W·m⁻² for females, each separated by 15 min of recovery) in the heat (35°C), which led to the older adults storing a greater amount of heat in their bodies relative to their younger counterparts (2-4, 20). Thereafter, two studies demonstrated that age-related impairments in the body’s ability to dissipate heat were heat load-dependent, such that impairments became evident at 200 W·m⁻² (7) and 190 W·m⁻² (6) in males and females, respectively. This was accomplished by using a novel incremental intermittent exercise model that consisted of exercise at progressively greater fixed rates of metabolic heat production (i.e., concept analogous to an incremental exercise test performed to determine an individual’s peak aerobic power [VO₂peak]). Although this work has started to define when aging matters, less is known about how whole-body heat dissipation may be improved with regular heat exposure in older adults.

Type 2 diabetes (T2D) is a metabolic disorder characterized by insulin resistance and relative (rather than absolute) deficiency of insulin (21) that is often diagnosed in older adults. The mean onset age is currently 54 years (22), however the age of diagnosis is currently on the decline (23). In general, T2D is often accompanied by multiple
comorbidities including obesity, dyslipidemia, hypertension and other cardiovascular diseases (24). Since the disease may go undetected for many years, the chronic elevations in glycemia related to delays in treatment of T2D can lead to micro- and macrovascular complications at/or shortly after diagnosis (i.e., neuropathy, nephropathy, retinopathy, etc.) (24). Because of their generally poor health status, individuals with T2D can be particularly vulnerable during exposure to heat stress. In fact, epidemiological data demonstrate that individuals with T2D are at an increased risk of heat-related illnesses and/or death during heat waves and/or extreme heat events relative to their healthy non-diabetic counterparts (25, 26, 40).

The existing research related to thermoregulatory function in individuals with T2D has mainly evaluated the local heat loss responses of the hands and feet to better define the level of neuropathy and other diabetes-related impairments (24). Incidentally, individuals with T2D demonstrate a diminished skin blood flow response (27-31), which appears to be dependent on the level of aerobic fitness of the individual, albeit the maximal level achieved is lower regardless (32). In line with these impairments, local sweating responses have also been shown to be typically reduced in adults with T2D (28, 33, 34), with only one study reporting no T2D-mediated impairment (35). Adults with T2D tend to demonstrate anhydrosis (i.e., absence of sweating) of the lower body, which is accompanied by euhydrosis (i.e., normal sweating) or hyperhidrosis (i.e., excessive sweating) of the upper body (33). Although the mechanisms underlying the lower heat loss responses are not well understood (24), there is evidence to believe that they are linked to a reduction in nitric oxide bioavailability (27, 31, 36). To date, very limited research has examined how these impairments in local heat loss responses may translate into meaningful differences in whole-body heat dissipation during passive and exercise-induced heat stress.
The aforementioned study by Kenny et al. (1) showed that habitually active older adults have a reduced capacity to dissipate heat during a 3-hour passive exposure to extreme heat (44°C and 30% relative humidity) compared to young adults. Importantly, these environmental conditions have been associated with an elevated risk of heat-related morbidity and mortality (37). The observed age-related impairments in heat dissipation led to greater elevations in body heat storage and core temperature, but similar cardiovascular strain between the young and older adults. No study to date, however, has been designed to evaluate whether habitually active older adults with T2D experience greater levels of hyperthermia (i.e., body heat storage and core temperature) and cardiovascular strain compared to their aged-matched healthy counterparts during the early stages of extreme heat events (i.e., the initial hours of heat exposure). This knowledge is particularly important since the initial hours of heat exposure during an extreme heat event have the largest impact on mortality rates in older individuals (38, 39), especially those with T2D (25, 26, 40).

Another recent study by Kenny et al. (41) demonstrated that sedentary older adults with T2D have a marked reduction in whole-body heat loss during 60 minutes of continuous moderate-intensity exercise (~185 W·m⁻² of metabolic heat production) relative to sedentary older adults without T2D in warm (30°C) conditions. This lower capacity to dissipate heat was due to a lower rate of evaporative heat loss for T2D, and consequently, they stored nearly 1.6-times more heat than their healthy counterparts over the duration of the exercise bout. However, it remains unclear if habitually active older adults with T2D still have impaired evaporative heat loss capacity, especially given that more physically active older adults with greater aerobic fitness maintain a greater capacity to dissipate heat relative to their sedentary counterparts (7). This information is essential since physical
activity is recognized as one of the best interventions to manage T2D due to its proven ability to improve cardiometabolic health (i.e., glycemic control, autonomic and vascular function, weight management and adiposity, physical capacity, and others) (24, 42-46). Furthermore, many intrinsic factors such as age (6, 7), sex (47), aerobic fitness (48, 49), and heat acclimation status (50, 51) alter the body’s ability to dissipate heat to a greater extent at higher exercise intensities and therefore heat load. Therefore, there is a possibility that any reductions in whole-body heat loss within habitually active older adults with T2D may become greater with increases in exercise-induced heat load, elevating the risk of heat-related morbidity and mortality when performing physical activity to manage their diabetes and/or during physical exertion in the heat, especially at greater intensities.

The process of heat adaptation, often referred to as heat acclimatization (i.e., natural environment) or heat acclimation (i.e., artificial environment), refers to the physiological adjustments that occur in response to repeated elevations in core temperature from physical activity/work and/or high ambient temperatures (52). In general, this process takes 10 to 14 days (52-55), with approximately 75-80% of the total physiological improvements evident after 7 days (50, 52). The physiological adjustments include enhanced sweating and skin blood flow responses (i.e., reduced onset threshold, increased sensitivity and greater maximal level achieved), reduced core and skin temperatures, improved fluid balance and cardiovascular control, as well as a reduced rating of perceived exertion for a given workload (52). A recent study by Poirier et al. (50) used the same incremental intermittent exercise model (three 30-min bouts of cycling at fixed metabolic heat loads of ~300, ~350, and ~400 Wm\(^{-2}\)) as described earlier (6, 7) to determine for the first time the extent to which heat acclimation affects whole-body heat exchange in young (~23 years) males. Using this model, it was reported that 14 days of heat acclimation increased whole-body
evaporative heat loss by 9, 12, and 18% at a metabolic heat load of ~300, ~350, and ~400 W m\(^{-2}\), respectively. Given that heat acclimation resulted in a ~6% increase in net dry heat gain, the net improvement in whole-body heat loss was ~8, ~8 and ~11% at each heat load, respectively. These findings showed that heat acclimation enhances whole-body heat dissipation in a heat load-dependent manner since the measured improvements in evaporative heat loss became greater with increasing levels of heat stress. Ultimately, the improved ability to dissipate heat resulted in a 26% decrease in body heat storage, with ~70% of the improvements evident after the first 7 days of heat acclimation. These results further confirmed the importance of the first week of heat exposure.

The functional adaptations to the sweating response, which is our primary avenue of heat dissipation in hot conditions, occur progressively as a function of the increase in body temperature (adaptation stimulus) with each successive day (52). The degree of improvement that transpires during a period of heat acclimation is thought to be dependent on an individual’s responsiveness to a given adaptation stimulus, which is reliant upon one’s accommodation “reserve” (52). This accommodation reserve is defined by the individual’s pre-adaptation baseline (i.e., starting point) and his genetically pre-determined physiological maximum (52). This concept draws a parallel to endurance training, whereby the improvements in \(\dot{V}O_{2\text{peak}}\) will be distinctly greater in sedentary individuals as compared to more physically active individuals, for the same training stimulus (56). Since older adults with T2D have been shown to possess a lower physiological capacity to dissipate heat compared to older adults without T2D prior to heat acclimation (i.e., pre-adaptation baseline) (41), it is possible that older adults with T2D have a greater accommodation reserve (i.e., capacity to adapt). Therefore, they may be more responsive to a given acclimation stimulus and thus exhibit a greater degree of adaptation to the sweating
response compared to their healthy non-diabetic counterparts. The opposite may also be possible such that adults with T2D may have an impaired ability to physiologically adapt for a given adaptation stimulus due to their overall decrease in physiological function (24), including but not limited to autonomic nervous system dysfunction (57), which can often pre-date or occur early after T2D diagnosis (58, 59). Nevertheless, a significant amount of research demonstrates that aerobic exercise training (i.e., walking, jogging, or cycling) can optimize glycemic control (fasting glycemia and HbA1c), improve cardiovascular function (i.e., blood pressure regulation, cardiac contractility, vascular function), reduce body mass, waist circumference and body adiposity in adults with T2D (24, 42-46). However, no study to our knowledge has been specifically designed to examine the extent to which thermoregulatory function may be enhanced by heat acclimation in this population. Once it is established at which heat load threshold T2D-mediated impairments in heat dissipation occur, further research is required to determine if heat acclimation can modify this response. It is also important to define if the magnitude of impairment, if any, can be mitigated with regular heat exposure.

1.2. Rationale and statement of the problem

It is well established that aging reduces the body’s ability to dissipate heat during heat stress, which is worsened in individuals with T2D. However, it currently remains unknown at what level of heat stress T2D-mediated impairments in whole-body heat loss become evident and whether these impairments become greater as the level of heat stress increases. This information is critical for establishing when individuals with T2D may be at an increased risk of heat and/or work-related injury (i.e., often a result of increased fatigue which accompanies high levels of hyperthermia). Furthermore, there is limited research
examining how aging and T2D affect an individual’s ability to physiologically adapt to the heat. Therefore, a comprehensive study directed at advancing our understanding of how heat acclimation may alter whole-body heat loss in older adults with and without T2D was required. Ultimately, it is important to determine whether regular exercise training in the heat may improve whole-body heat dissipation in older adults with and without T2D.

1.3. Objectives

The objectives of this thesis are to: 1) determine if habitually active older adults with T2D, compared to matched individuals without T2D, exhibit a reduced capacity to dissipate heat and therefore greater levels of hyperthermia and cardiovascular strain during passive exposure to extreme heat (Study 1); 2) determine the threshold at which T2D-mediated impairments in heat loss are evident and whether impairments become greater with increasing levels of heat stress (Study 2); and 3) determine the extent to which short-term heat acclimation (exercise training in the heat) reverses or enhances T2D-related impairments in heat loss in habitually active older males (Study 3).

To achieve the first objective, we compared local and whole-body thermoregulatory responses as well as cardiovascular responses between individuals with and without T2D matched for age and physical characteristics (i.e., body height, mass, surface area) before and after a 3-hour passive exposure to extreme heat. The second objective was accomplished by comparing local and whole-body thermoregulatory responses between adults with and without T2D matched for age, physical characteristics (same as previous), and \( \dot{V}O_{2\text{peak}} \) during exercise performed at increasing levels of heat stress (i.e., successive exercise bouts at increasingly greater fixed rates of metabolic heat production). The third objective was achieved by comparing local and whole-body
thermoregulatory responses between older adults with and without T2D with similar age, physical characteristics (same as previous), and \( \dot{V}O_{2\text{peak}} \), during exercise performed at increasing levels of heat stress performed before and after a 7-day heat acclimation protocol (daily moderate-intensity exercise training in the heat).

1.4. Hypothesis

1.4.1. General hypothesis of the thesis

It was hypothesized that T2D would impair the body’s ability to dissipate heat above a specific heat load threshold in non-heat acclimated older adults, with the magnitude of impairment becoming greater with increasing levels of heat stress. However, we hypothesized that short-term heat acclimation would mitigate T2D-mediated reductions in whole-body heat dissipation.

1.4.2. Specific hypotheses of the thesis

Specifically, it was hypothesized that:

**Study 1:** Individuals with T2D would experience higher levels of hyperthermia compared to their age-matched healthy counterparts due to lower whole-body evaporative heat loss and therefore greater body heat storage during 3 hours of passive heat exposure. In parallel, it was hypothesized that adults with T2D would experience greater levels of cardiovascular strain relative to their healthy controls.

**Study 2:** Individuals with T2D would demonstrate significantly lower whole-body evaporative heat loss relative to their age-matched healthy counterparts for a given exercise-induced heat load and/or the threshold for these differences would occur at a similar or greater heat load than in our previous work (~185 W m\(^{-2}\)) (41) given that habitually active older adults with higher \( \dot{V}O_{2\text{peak}} \) have been shown to maintain greater heat
loss capacity relative to their lesser fit counterparts (7). Moreover, it was hypothesized that greater impairments would be measured with increasing heat loads, which would result in a greater change in body heat storage for a given heat load in those with T2D relative to those without T2D.

**Study 3:** Whole-body evaporative heat loss would be increased at all heat loads following 7 days of short-term heat acclimation in older males with and without T2D, albeit the improvements would be greater with each increasing level of heat stress. As a result of the enhanced capacity to dissipate heat, both groups would store less heat for a given exercise-induced heat load.

### 1.5. Relevance of the study

In 2017, it was estimated that 451 million people aged 18 to 99 years were living with diabetes, which represents a global diabetes prevalence of 8.4% (60). Of these cases, it is conservatively estimated that ~49% of the people with diabetes have not been diagnosed. By 2045, the number of people living with diabetes, primarily between the ages of 40 and 59 years, is projected to increase to a disturbing 693 million worldwide, which would represent a global diabetes prevalence of 9.9% (60), with T2D accounting for approximately 85 to 95% of all diabetes cases in high- and middle-income countries.

While the most vulnerable populations during extreme heat events are older adults, those with T2D are at an increased risk of heat-related illness (i.e., heat exhaustion, heatstroke, and others) and death as compared to their nondiabetic counterparts (25, 61). Considering the number and severity of extreme heat events is projected to increase in coming years (62), the results from this thesis are timely as they greatly improve our understanding of the effects of T2D on the body’s ability to dissipate heat during heat stress.
in older adults. Our findings will assist health professionals in making evidence-based clinical decisions during heat stress events, which could depend on the time of year (i.e., spring vs. summer) and/or other factors such as the level of physical activity/work performed on a regular basis (i.e., job requirements, physical training, etc.). Moreover, this thesis provides more scientific evidence to policy makers to develop and implement T2D-specific heat exposure guidelines and recommendations aimed at reducing the incidence of heat-related morbidity and mortality in this vulnerable population group.
CHAPTER 2
REVIEW OF THE LITERATURE
2.1. Human thermoregulation

2.1.1. Heat balance

Healthy humans can maintain core temperature within reasonably narrow limits (~37°C), independent of variations in environmental conditions and/or levels of physical activity. Maintaining thermal homeostasis is dependent upon the body’s ability to continuously adjust physiological mechanisms to attain equilibrium between the heat produced within the body, the heat gained from the environment, and the heat lost to the environment (63). This dynamic balance is best represented by the heat balance equation(64):

\[ S = M - (\pm W) \pm (R + C) - E \] \[ W \cdot m^{-2} \] \[ (1) \]

Where:
- \( S \) is the rate of body heat storage;
- \( M \) is the rate of metabolic energy expenditure;
- \( W \) is the rate of external work which is positive if it is being performed against an external force, or negative for eccentric or negative work;
- \( R \) is the rate of radiant heat exchange;
- \( C \) is the rate of convective heat exchange and;
- \( E \) is the rate of evaporative heat exchange.

It follows that the amount of heat stored in the body \((S)\), and the corresponding increase in core body temperature, is dependent on the rate of metabolic heat production \((M \pm W)\) and total heat loss \((R + C - E)\). In a thermoneutral environment, a positive rate of body heat storage \((S)\) will occur when the rate of metabolic heat production exceeds the rate of total heat loss \((i.e. M \pm W > R \pm C - E)\). Likewise, in a hot environment, a positive rate of body heat storage \((S)\) will occur if the combined rates of metabolic heat production and dry heat gain exceed the rate of evaporative heat loss \((i.e. M \pm W + R + C > E)\), eventually resulting in an increase in core temperature. In contrast, a negative rate of body heat storage \((S)\) will occur when the rate of total heat loss exceeds the rate of metabolic heat production.
(i.e. \( M \pm W < R + C – E \)), leading to a reduction in core temperature. If left unchecked, an increase or decrease in body heat storage \((S)\), and correspondingly an increase or decrease in core temperature, can lead to hyperthermia or hypothermia respectively, both of which can result in death if not addressed immediately \((65, 66)\). In order to avoid such situations, the preoptic anterior hypothalamus, which is the thermoregulatory center of the human body \((67, 68)\), integrates afferent thermal information from peripheral (i.e., epidermis, abdominal cavity, muscles, and major blood vessels) and central (i.e., brain and spinal cord) temperature sensitive receptors (thermoreceptors) to appropriately alter thermoeffector responses in order to maintain a stable core temperature \((67-72)\). When a thermal challenge is sensed peripherally and/or centrally, the effector responses of sweating and skin blood flow are activated to elevate the rate of evaporative and dry heat loss. The amount of heat stored in the body, and the corresponding increase in core temperature, is dependent on the body’s capacity to maintain a balance between the heat produced within the body (and/or heat gained from the environment) and the heat lost to the environment.

2.1.2. Mechanisms of heat dissipation

The human body depends on vasomotor tone and sudomotor activity to remain in heat balance. Vasomotor tone refers to changes in diameter of blood vessels, which during heat stress will be a reflex vasodilatory response to promote greater skin blood flow. This is accomplished by an increase in cardiac output as well as a redistribution of blood from the renal and splanchnic vascular beds to the skin \((73)\). The increase in skin blood flow enhances the rate of heat loss by increasing convective heat transfer from the core to the skin where it can be lost to the environment \((74)\). This reflex increase in skin blood flow is neurologically mediated by sympathetic cholinergic nerves that release acetylcholine as
well as an un-identified co-transmitter (75). The putative cholinergic neurotransmitters include vasoactive intestinal peptide (76-78), substance P (79), calcitonin gene-related peptide (77), and histamine/neurokinin receptor activation (78, 80, 81). These neurotransmitters activate secondary messenger pathways such as nitric oxide (NO)- and cyclooxygenase (COX)- dependent mechanisms to partly mediate increases in skin blood flow (78, 79, 81). A sudden increase in metabolic heat production (i.e. exercise) requires the activation of the sudomotor response as the increase in skin blood flow is unable to offset the increase in metabolic heat load (82).

Sudomotor activity, which is the increase in sweat production followed by the evaporation of sweat from the skin surface, allows the body to dissipate large amounts of heat. The human body has apocrine and eccrine sweat glands (83). Apocrine sweat glands are present in specific anatomic areas (i.e., ear canal, nostrils, armpits, groin, and others), always associated with hair follicles, and secrete a viscous fluid that does not contribute to heat dissipation. In contrast, the eccrine glands present over the skin surface secrete a serous fluid that contributes to heat dissipation. The neurotransmitter acetylcholine is also released by sympathetic nerves that innervate eccrine sweat glands in order to activate sweat production (84). Once acetylcholine is released, it is rapidly hydrolyzed by the enzyme acetylcholinesterase and muscarinic receptors are stimulated to allow an influx of calcium ions to activate the entry of sodium and chloride ions into the cell, creating an osmotic gradient that allows water to flow from the plasma into the sweat gland (13). Once the water enters the duct of the sweat gland, it can be expelled on the skin surface for evaporation.
2.1.3. Thermoeffector response – mean body temperature relationship

The control of sweating and skin blood flow are dependent on changes in skin (85) and core temperature (86, 87). Hence, mean body temperature (the weighted sum of core and skin temperatures) is used when examining the effects of various factors (i.e., aging, sex, aerobic fitness, heat acclimation etc.) on the control of sweating and skin blood flow (87, 88). The influence of these factors has been studied by evaluating the thermoeffector response – temperature relationship consisting of three parts: the onset threshold, the thermosensitivity, and the plateau of the response (Figure 1, left panel).

First, the mean body temperature at which increases in sweating and skin blood flow occur represents the onset threshold of the response (74, 82). Second, the thermosensitivity corresponds to the slope of the line which designates the increase in effector response as a function of increases in mean body temperature (74). Third, the plateau corresponds to the level portion of the line, representing a balance (when heat production is equal to heat loss) or a maximal (no further increase can occur despite a further increase in mean body temperature) response of sweating or skin blood flow. Changes in the onset threshold have been attributed to central modulations (i.e. hypothalamus), while changes in thermosensitivity have been associated with peripheral alterations (i.e., sweat glands, skin vasculature) of thermoeffector responses (87, 89). In contrast, the plateau level achieved for sweating and skin blood flow has been used to evaluate an individual’s maximal capacity. Altogether, a lower onset threshold, an increase in thermosensitivity and an increase in the plateau/maximal level achieved will enhance thermoregulatory capacity (i.e., heat acclimation), while a greater onset threshold, lower thermosensitivity, and reduced plateau/maximal level will decrease an individual’s
thermoregulatory capacity (i.e., aging, inactivity and/or non-exposure to the heat) (Figure 1, right panel).

![Figure 1](image)

Figure 1. Schematic representing changes in thermoeffector responses to changes in mean body temperature during a thermal challenge (right panel) and examples of improvements (1) and impairments (2) in thermoeffector responses as a function of changes in mean body temperature.

### 2.2. Aging and thermoregulation

While some studies demonstrate no age-related impairments in the body’s ability to dissipate heat (90-93), others report a reduction in heat dissipation during exercise in the heat as evidenced by attenuations in local and/or whole-body heat loss (e.g., greater onset threshold, reduced thermosensitivity, and/or plateau/maximal level achieved) and/or greater increases in core body temperature or body heat storage (2-4, 6, 7, 9, 11, 94-98). These age-related reductions in heat dissipation are thought to become greater when compounded by factors such as low aerobic fitness (as assessed by VO\textsubscript{2peak}), increased body adiposity, and the presence of chronic diseases (i.e., T2D, cardiovascular disease, etc.), all of which
commonly occur with aging (99, 100). In order to negate the influence of such factors on thermoregulatory responses in older adults, studies have attempted to match young and older participants according to key characteristics (4, 11, 90).

Another important experimental limitation of numerous studies showing age-related differences in heat loss responses is that young and older adults performed exercise at the same percentage of $\dot{V}O_2_{\text{peak}}$ (101-103). Considering that older adults usually have a lower $\dot{V}O_2_{\text{peak}}$ than their younger counterparts, an underestimation of the age-related reduction in heat loss was likely between young and older adults. To avoid this problem, researchers started matching young and older adults based on $\dot{V}O_2_{\text{peak}}$ or used fixed work rates regardless of differences in $\dot{V}O_2_{\text{peak}}$ (4, 104). However, this experimental design may also confound the true age-related impairments in the body’s capacity to dissipate heat as the older participants matched for physical activity and/or $\dot{V}O_2_{\text{peak}}$ might not be representative of the general aging population. As such, it remains unclear what the typical age-related impairments in the body’s capacity to dissipate heat may be and how maintaining an active lifestyle and/or high level of aerobic fitness may help attenuate the impairments in heat loss associated to aging per se.

2.2.1. Aging and skin blood flow

Healthy aging has been shown to decrease skin blood flow during heat stress (15, 16, 93, 105, 106). This decrease in vasodilatory capacity has been deemed a true physiological consequence of the aging process since reductions in skin blood flow are also apparent when older adults are matched for aerobic fitness (93), acclimation state (107), and hydration status (108), with their younger counterparts. Although some central cardiovascular changes partly mediate the reduction in skin blood flow in older adults (i.e.,
reduced cardiac output and less blood redistributed from splanchnic and renal vascular beds) (12), some peripheral changes take place such as a reduction in the thermosensitivity of the response (14) and structural alterations to the skin vasculature (92). The age-related impairments in skin blood flow have been mainly attributed to a reduction in NO bioavailability. This has been associated to a decrease in NO synthesis due to reductions in functional L-arginine and BH₄ availability as well as an increase in NO breakdown through oxidative stress (109). These findings are supported by studies showing improvements in skin blood flow in older adults following interventions aimed at increasing NO bioavailability (15-18). In addition, maximal skin blood flow decreases with increasing age (110), which reflects changes in the structural properties of the blood vessels. These include hypertrophy of vascular smooth muscles and a reduction in the number of capillaries (111).

2.2.2. Aging and sweating

Local sweating responses have been shown to be lower in older adults relative to young adults (11, 92). The attenuated sweat rates measured in older adults could be due to a reduced cholinergic sensitivity (8, 9), a lower thermosensitivity (10), and age-related changes in the structure of the sweat gland (11), all of which represent peripheral alterations. The onset threshold, which signifies a central mechanism, can either be augmented (6) or unchanged with increasing age (96, 97). Lower sweat rates in older adults have also been associated with a reduced sweat gland output as opposed to a reduction in the number of heat activated sweat glands (11), further suggesting that peripheral mechanisms are the reason for the age-related decrease in sweating. Recently, the lower sweat rates observed in older adults have also been in part, associated to an attenuation in NO-dependent sweating (19).
Similar to skin blood flow, it remains unclear whether the decrease in sweating with age is due to a gradual reduction in \( \dot{V}O_2 \text{peak} \) or whether it is a true age-related impairment (11, 94, 95, 98, 104, 112). For example, one study showed no difference between young (28-37 years) and older (55-60 years) adults matched for \( \dot{V}O_2 \text{peak} \) in a thermoneutral (21°C, 43% relative humidity), hot-dry (40°C, 20% relative humidity), and hot-humid (30°C, 80% relative humidity) environments, albeit the rise in the sweating response was slower in the older adults in the hot environments (112). Using multiple regression analysis, Havenith et al. (104) examined the relative influence of age compared to other individual factors (\( \dot{V}O_2 \text{peak} \), physical activity level, anthropometry, adiposity) on thermoregulatory responses during 60 min of light-intensity (fixed workload of 60 W) exercise in 35°C and 80% relative humidity in a heterogeneous sample of 56 subjects where there was no interrelation between age (20 to 73 years) and \( \dot{V}O_2 \text{peak} \) (1.8 to 4.4 l\( \text{min}^{-1} \)). They reported that age did not influence the sweating response, the rise in rectal temperature, or the amount of heat stored in the body. Rather, their findings suggested that \( \dot{V}O_2 \text{peak} \) may have a greater influence on sweating and overall thermoregulatory function than age \textit{per se}.

Another important point to consider is that some heterogeneity exists in the attenuation of local sweat rate in older adults. For example, older adults have been shown to have attenuated sweat rates on the thigh and upper back, yet no difference on the forehead, chest and forearm compared to younger adults (97, 113). On the other hand, another study showed lower sweat rates on the forehead and calf, but no difference on the thigh and chest (96). Given these regional disparities in local sweating responses, whole-body direct calorimetry has recently been used to assess whether whole-body sudomotor activity (as assessed by measuring whole-body evaporative heat loss) is impaired with increasing age (2-4, 6, 7). This method is widely considered as the most accurate technique
to measure whole-body heat loss since it measures the combined activity of the human body’s 2-4 million sweat glands (114, 115).

2.2.3. Aging and whole-body heat loss

Passive heat stress

Recent studies have examined age-related changes in whole-body heat loss during passive heat exposure. First, Stapleton et al. (5) examined the effects of age on whole-body heat dissipation using direct calorimetry during passive exposure to environmental conditions representative of the upper temperatures experienced in Canada. Young (~21 years) and older adults (~65 years) matched for body weight and body surface area rested for 2 hours in a hot-dry (36.5°C and 20% relative humidity) or hot-humid (36.5°C and 60% relative humidity) environment. In both conditions, the rate of evaporative heat loss was similar between age groups; however, the rate of dry heat gain was ~5 W m⁻² greater for the older adults during both conditions. Because of this greater dry heat gain, the amount of heat stored over the 2-hour exposure was 1.6 and 1.3-fold greater in the older adults relative to their younger counterparts in the hot-dry and hot-humid conditions, respectively. These findings show that older adults experience greater levels of whole-body hyperthermia during short exposures to dry and humid heat, which may place them at increased risk of heat-related illness and/or injury. As a follow-up study, Kenny et al. (1) examined whether age-related differences in whole-body evaporative heat loss would be evident during a longer, more extreme heat exposure. To do so, thirty young (18-30 years) and thirty older (55-73 years) adults underwent a 3-hour passive exposure to extreme heat (44°C and 30% relative humidity). The older adults demonstrated an attenuated increase in evaporative heat loss during the first 30 min of exposure compared to their younger counterparts. Thereafter,
the older adults were unable to compensate for a ~6 W m\(^{-2}\) greater dry heat gain throughout the rest of the exposure. As a result of their inability to achieve heat balance, the older adults had a 1.8-fold greater change in body heat storage relative to the young adults. Altogether, these findings demonstrate that older individuals experience greater levels of thermal strain during extreme heat events thereby increasing the risk of adverse health events.

**Exercise heat stress**

Direct calorimetry has recently been used to examine age-related changes in whole-body heat loss during exercise in the heat. First, physically active young (~22 years) and middle-aged adults (~45 years) matched for $\dot{V}O_2_{peak}$ (~51.9 mLO\(_2\) kg\(^{-1}\) min\(^{-1}\)), body surface area (~2.06 m\(^2\)), and body composition (~20% body fat) showed a similar capacity to dissipate heat during 90-min of cycling at a fixed rate of metabolic heat production (~140 W m\(^{-2}\)) at three different environmental heat loads (30, 35 and 40°C) (90). The amount of heat stored between groups was similar during exercise in each of the environmental conditions. The lack of difference may have been due to the combined metabolic and environmental heat loads not exceeding the individual’s capacity to dissipate heat.

More recently, Larose et al. published three studies (2-4) that found age-related impairments in the body’s physiological capacity to dissipate heat to occur as early as the age of 40 years during intermittent exercise at a fixed rate of metabolic heat production of 200 W m\(^{-2}\). This attenuation in the body’s physiological capacity to dissipate heat led to greater body heat storage for older males and females compared to their younger counterparts. Despite showing true age-related impairments in the body’s physiological capacity to dissipate heat, the experimental protocol used did not allow us to determine
whether these impairments were only evident above a specific heat load threshold (as defined by the sum of metabolic heat production and dry heat exchange). It also remained unclear whether the reduction in whole-body heat loss would become greater with increasing heat loads, and whether it would be apparent at lower heat loads.

As a follow-up to the above studies, Stapleton et al. (7) examined whole-body evaporative heat loss in ten young (~21 years), ten middle-aged (~48 years), and ten older (~65 years) males matched for body surface area (~1.98 m²) using an incremental intermittent exercise protocol that consisted of three 30-min cycling bouts at progressively greater fixed rates of metabolic heat production equal to 150, 200, and 250 W m⁻² in the heat (40°C and 15% relative humidity). Each exercise bout was separated by 15 min of recovery. Also included was a group of ten middle-aged trained males (~49 years) matched for body surface area with all groups and for \( \bar{V}O_2 \text{peak} \) with the young group (~51.0 mLO₂·kg⁻¹·min⁻¹). The results showed that whole-body evaporative heat loss was significantly lower in middle-aged untrained and older males compared to the young and middle-aged trained males at the mid (200 W m⁻²) and high (250 W m⁻²) heat loads employed. This was due to a decrease in the thermosensitivity of the response as the onset threshold was similar between groups. In contrast, no differences in evaporative heat loss were measured between the young and middle-aged trained males, showing that age-related impairments in heat loss capacity can be minimized when maintaining a high level of aerobic fitness (as defined by \( \bar{V}O_2 \text{peak} \)) in middle-aged males. Altogether, the middle-aged untrained and older adults stored 1.5- and 1.6-fold more heat than the young males over the entire protocol. These findings demonstrated that age-related impairments in the body’s physiological capacity to dissipate heat are evident at exercise-induced heat loads as low as 200 W m⁻² when performed in hot, dry conditions, in middle-aged untrained and older
males. Moreover, it was shown for the first time that the magnitude of age-related impairments in heat loss becomes greater as the heat load increases. This places older adults at further risk of suffering from heat-related illnesses, especially as the combined metabolic and environmental heat load increases.

Using the same intermittent protocol with the exception of lower fixed rates of metabolic heat production (150, 190, and 235 W·m⁻²), Stapleton et al. (6) examined whole-body evaporative heat loss in ten young (~23 years) and ten older (~58 years) females matched for body surface area (~1.69 m²) and Vo2peak (~39.4 mLO₂·kg⁻¹·min⁻¹). They reported an attenuated rate of whole-body evaporative heat loss in the older females at the mid (190 W·m⁻²) and high (235 W·m⁻²) heat loads employed, with a greater impairment measured with each increasing heat load. The lower rates of evaporative heat loss in the older females were due to a greater onset threshold, a reduced thermosensitivity and lower maximum plateau level achieved. These observations show that central and peripheral adjustments are responsible for the reduced rate of heat loss in older females. In sum, these findings indicate that habitually active older females have an impaired heat loss capacity during exercise-induced heat loads as low as 190 W·m⁻², irrespective of one’s fitness level.

2.3. Type 2 diabetes and thermoregulation

Type 2 diabetes, which is most often diagnosed in older adults, is a chronic disease that is characterized by insulin resistance (relative rather than absolute deficiency) (116) and chronic hyperglycemia (117). Risk factors such as obesity, poor diet, sedentary lifestyle, advancing age, family history of diabetes, ethnicity, as well as gestational diabetes are considered to be precursors to the disease (60). Furthermore, T2D is often
accompanied by other comorbidities such as dyslipidemia, metabolic syndrome, hypertension, as well as other cardiovascular diseases (116). If not well controlled, T2D can lead to micro- and macro-vascular complications such as nephropathy, retinopathy, and autonomic and/or peripheral neuropathy (116). As a result of these comorbidities and complications, adults with T2D have a 56% greater chance of hospitalization and/or death during heat waves and extreme heat events relative to their healthy non-diabetic counterparts (25, 26)

2.3.1. Type 2 diabetes and skin blood flow

Type 2 diabetes negatively alters skin vasculature which decreases NO bioavailability, an important modulator of skin blood flow. As a consequence, skin blood flow may be reduced in individuals with T2D when exposed to pharmacological stimuli (27, 31, 118) as well as during local (28, 29, 119, 120) or whole-body heating (28, 30, 121) compared to their matched counterparts. Since most studies examining skin blood flow in individuals with T2D have mainly evaluated responses on the hands and feet, further studies are required to determine the extent to which the body’s thermoregulatory capacity changes in this population.

Endothelium-dependent and endothelium-independent vasodilation in the forearm has been shown to be reduced in individuals with T2D (27, 31, 118). The reflex increase in skin blood flow in response to the administration of methacholine chloride (31) and sodium nitroprusside (27, 31, 118) was reduced in individuals with T2D, indicating an impairment in endothelium-independent vasodilation. Other studies showed that individuals with T2D have a reduced skin blood flow response during local heating (41 and 44°C) (27, 118) and during the infusion of acetylcholine (endothelium-dependent vasodilation) compared to
their matched controls without diabetes. In the two latter studies, the impairments in skin blood flow were greater in individuals that had T2D-related complications (i.e., neuropathies), which generally also meant a greater duration since the initial diagnosis.

Using microdialysis to infuse $\text{N}^\text{G}$-nitro-$\text{L}$-arginine methyl ester, an NO-synthase inhibitor, and lactated Ringer’s solution (control site), Sokolnicki et al. (36) showed that the relative contribution of NO to skin vasodilation was similar between individuals with and without T2D, albeit cutaneous vascular conductance was reduced by 20-25% during local heating (43˚C) and the infusion of sodium nitroprusside for the individuals with T2D. Similar findings were also observed using the same protocol during whole-body heating (121). It was also shown that the onset threshold for skin blood flow was greater in individuals with T2D during whole-body heating, thereby proposing that a central mechanism responsible was, in part, responsible for the T2D-related decrease in skin blood flow. Altogether, these findings show that the body’s ability to regulate skin blood flow in response to a thermal challenge is altered, which seems to be dependent on the presence of complications and/or duration of the disease.

2.3.2. Type 2 diabetes and sweating

Limited studies have examined how T2D affects the sweating response in the context of thermoregulation, with most studies examining sweating in the context of diagnosing diabetic neuropathy. Of these studies, most report an attenuated sweat rate in individuals with T2D (28, 33, 34) albeit one study showed that the number of heat activated sweat glands and the corresponding sweat gland output was comparable between individuals with and without T2D during acetylcholine iontophoresis (35).
When the sweating response was evaluated during whole-body heat exposure, individuals with T2D showed a reduced sweat rate (28, 33). Similarly to skin blood flow, the presence of neuropathy seems to be an important factor in attenuating sweat output as one study reported that 94% of individuals with T2D with neuropathy showed sweating anomalies during passive heat stress (44°C and 45% relative humidity) (33). These anomalies included a reduced sweating response on the lower body, with complete anhydrosis observed in certain cases. Furthermore, there seems to be a certain degree of heterogeneity in the observed attenuations in sweat rate in individuals with T2D. Petrofsky et al. (28) reported a lower sweat rate on the head, chest, leg and forearm in individuals with T2D compared to matched controls during passive heat exposure (39°C). When participants were asked to perform a handgrip exercise at 40% of their maximal voluntary contraction in the heat, individuals with T2D had attenuated sweat rates on the arms and legs while their sweating response was greater on the forehead compared to their matched counterparts (28). Considering the discrepancy between local sweat sites and the lack of studies evaluating the sweating response in the context of thermoregulation, more research is required to determine the extent to which whole-body evaporative heat loss (and therefore whole-body sweat production) may be altered in individuals with T2D.

Current evidence suggests that sweating impairments in individuals with T2D may be due to peripheral changes to the sweat glands themselves (33, 122, 123), with greater alterations observed with longer duration of T2D and/or when patients exhibit poor glucose control (33, 123) or have neuropathy (123). In fact, studies show that individuals with T2D have less innervated sweat glands than their matched healthy counterparts (122, 123), which seems to be inversely correlated to an individual’s HbA1c (123). As eluded to
previously in the context of skin blood flow, the reduction in sweat gland output could also be the result of a reduction in NO bioavailability (124, 125).

2.3.3. Type 2 diabetes and whole-body heat loss

Passive heat stress

To the best of our knowledge, no study to date has assessed the effect of T2D on whole-body heat loss during passive heat exposure. However, since adults with T2D tend to demonstrate further decreases in skin blood flow (30, 121, 126-128) and sweating (28, 129) measured at single sites across the body (i.e., forehead, forearm, chest, back, thigh, feet and hands) compared to their age-matched counterparts, it is possible that they possess a reduced rate of whole-body heat dissipation while resting in the heat. This hypothesis is supported by one study that reported a reduced maximal increase in both sweating and skin blood flow in older adults with T2D relative to their non-diabetic counterparts during progressive increases in environmental heat load (~22 to 42°C), which led to a greater increase in core temperature after 30 min of exposure (28, 130). However, it remains to be determined how these observations may translate into differences in whole-body heat loss (evaporative heat loss and dry heat exchange) and body heat storage during more prolonged passive heat exposures. Furthermore, studies have shown that adults with T2D tend to have a lower absolute level of cardiovascular function (131) as evidenced by impaired vascular function (30, 121, 126-128), lower increases in cardiac output (132), altered blood pressure regulation (133-135), and reduced autonomic function (136) compared to non-diabetic adults of the same age. These impairments in cardiovascular function could be exacerbated by greater heat strain associated with potential reductions in heat dissipation during exposure to hot environments, which could ultimately explain why individuals with T2D
are at increased risk of heat-related morbidity and mortality compared to the general population during heat waves (25, 26, 40).

**Exercise heat stress**

To our knowledge, only one study has evaluated the effect of T2D on whole-body heat loss and therefore the level of hyperthermia experienced during exercise in the heat. Using direct calorimetry, Kenny et al. (41) had ten sedentary older adults with (HbA1c of 7.3%) and without T2D matched for age (~56 years), sex (6 males and 4 females), body surface area (~2.01 m²), and aerobic fitness (~25.0 mLO₂·kg⁻¹·min⁻¹) exercise for 60 minutes at a fixed rate of metabolic heat production of 185 W·m⁻² in warm conditions (30°C and 20% relative humidity). The individuals with T2D demonstrated an attenuated whole-body evaporative heat loss from 15-min to the remainder of the 60-min exercise bout. While no difference was observed for the onset threshold of evaporative heat loss between groups, the thermosensitivity of the response was reduced in the individuals with T2D. This impaired evaporative heat loss response led to 35% more heat stored in the T2D group. Despite this greater amount of heat stored, no differences were measured in core temperature between groups. Moreover, despite the reported differences in the literature, the impaired whole-body heat loss was not paralleled by similar differences in local sweating (upper back) or skin blood flow (forearm) measurements. Discrepancies between local and whole-body heat loss responses as well as between core temperature and body heat storage measurements are well documented (114), ultimately making it difficult to determine the level of impairment in thermal strain. The lack of differences in local heat loss measurements between individuals with T2D and their healthy counterparts does not mean that they do not have any impairments in local sweating and skin blood flow, but
rather that the lack of difference may only reflect regional differences in those responses (28, 33).

Since the previous study examined whole-body heat loss in sedentary older adults with T2D, it therefore remains uncertain whether habitually active older adults with T2D still have impaired thermoregulatory function. This question is fundamentally important, as physical activity is a foundation in T2D management due to its ability to improve glucose regulation, cardiovascular function, and aerobic fitness (and overall physical capacity) as well as delay/prevent T2D-related complications (i.e., neuropathies) (24, 43-46). Moreover, it has recently been reported that habitually active older adults with higher VO$_2$peak possess greater heat loss capacity relative to their sedentary counterparts, which can attenuate age-related impairments in thermoregulatory function (7). It is therefore possible that adults with T2D who perform regular physical activity and possess a higher VO$_2$peak may have a thermoregulatory advantage compared to more sedentary adults with T2D with a lower VO$_2$peak. In addition, several other individual factors (e.g., age, sex, aerobic fitness, others) modulate heat dissipation to a greater extent at higher exercise-induced heat loads (6, 7, 47-49). Therefore, it is conceivable that any impairment in whole-body heat loss among habitually active older adults with T2D may be exacerbated with increasing heat load, which would increase the risk of heat-related illnesses and/or death when performing physical activity to manage their disease, especially at higher intensities. However, this also remains unclear since our previous study examining the effects of T2D on whole-body heat loss during exercise limited its assessment to a single exercise-induced heat load (41).
2.4. The influence of aerobic fitness, physical activity and heat acclimation

2.4.1. Aerobic fitness and physical activity

Maintaining an active lifestyle and a high aerobic fitness level is important in preserving good health and physical capacity. However, natural aging has been associated with a ~7% decrease in \( \dot{V}O_{2\text{peak}} \) per decade (137). Despite the age-related decrease in aerobic fitness, studies show that performing regular endurance exercise may induce partial heat acclimation (138, 139), which is characterized by enhanced heat loss responses (sweating and skin blood flow – reduced onset threshold, greater thermosensitivity and/or greater plateau/maximal level achieved for a given heat load), as well as attenuated heart rate, core and skin temperatures, and perceived exertion during exercise in the heat (52). In fact, performing regular physical activity throughout the lifespan and/or maintaining a high \( \dot{V}O_{2\text{peak}} \) may help attenuate the age-related impairments in heat loss capacity (7, 8, 92, 140), yet this has not always been the case (3, 6, 11).

The findings by Larose et al. (3) and Stapleton et al. (6) contradict the previously mentioned conclusions made by Havenith et al. (104) such that a similar whole-body evaporative heat loss (and thus sudomotor activity), and therefore change in body heat storage, should have been measured between young and older females bearing in mind that both groups had a similar \( \dot{V}O_{2\text{peak}} \). Considering that older females in both studies showed an attenuated whole-body heat loss, it appears that there is a true age-related impairment in heat loss capacity. Furthermore, if \( \dot{V}O_{2\text{peak}} \) was a better predictor of the body’s capacity to dissipate heat than aging \textit{per se}, responses between young and middle-aged males should have been almost identical, with a greater separation between the middle-aged and older males in the studies by Larose et al. (2, 4). Therefore, these findings further support the fact
that age-related impairments in the body’s physiological capacity to dissipate heat do exist independent of one’s aerobic fitness level. In contrast, the more recent study by Stapleton et al. (7) demonstrated that maintaining a high \( \bar{V}O_{2\text{peak}} \) can help delay age-related impairments in the body’s capacity to dissipate heat in middle-aged males. Furthermore, recent studies from our laboratory showed that aerobic fitness modulates heat loss in a heat-load dependent manner in young males (~22 years) (48) and females (~21 years) (49) such that young, highly fit males (~62 mLO\(_2\)-kg\(^{-1}\)-min\(^{-1}\)) and females (~53 mLO\(_2\)-kg\(^{-1}\)-min\(^{-1}\)) display a greater heat loss capacity at exercise-induced heat loads \( \geq 250 \text{ W.m}^{-2} \) and \( \geq 240 \text{ W.m}^{-2} \), respectively, compared to their lesser trained counterparts (males: ~40 mLO\(_2\)-kg\(^{-1}\)-min\(^{-1}\); females: ~36 mLO\(_2\)-kg\(^{-1}\)-min\(^{-1}\)). In contrast, aerobic fitness has not been considered a possible factor in any of the studies thus far as the individuals with and without T2D had similar \( \bar{V}O_{2\text{peak}} \) and physical characteristics. Taken together, it remains unclear whether having a high \( \bar{V}O_{2\text{peak}} \) or maintaining a high level of physical training (training status) better maintains an individual’s ability to dissipate heat, especially as we age and/or have T2D.

### 2.4.2. Heat adaptation

Heat adaptation, frequently referred to as heat acclimatization (i.e., naturally induced) or heat acclimation (i.e., artificially induced), refers to the marked physiological adjustments that ensue in response to repeated elevations in core and/or skin temperatures from either exercise, high ambient temperatures, or a combination of both (52). The typical physiological adjustments associated with natural or artificial heat adaptation include enhanced sweating and skin blood flow responses (lower onset threshold and greater thermosensitivity), reduced core and skin temperatures, as well as improved fluid balance (i.e. increased plasma volume, retention of electrolytes, etc.) and cardiovascular control.
(i.e. attenuated heart rate, improved contractility of the heart, etc.) (17, 52). However, the magnitude of improvement is dependent on the type (i.e., passive vs. exercise-induced heat stress, dry vs. humid heat exposure), intensity, duration, frequency, and number of heat exposures (17, 52). Altogether, these adaptations improve an individual’s level of thermal comfort, reduced perceived physical exertion when physical work is performed in the heat, as well as improved exercise capacity (Figure 2).

Figure 2. Time course of human adaptations to repeated heat exposure. Within this first week of exercise heat acclimation, plasma volume expands and heart rate decreases during exercise at a given work rate. Perceptually, the rating of thermal comfort improves. From a thermoregulatory perspective, core and skin temperature are reduced during exercise at a given work rate, whereas sweat rate increases. Consequently, aerobic exercise capacity is increased. Reproduced with permission from Périard et al (55).

Heat adaptation has been characterized into three stages (52): physiological accommodation, short-term and long-term adaptation. Physiological accommodation refers to the acute physiological response that we observe in sedentary individuals, who are rarely exposed to the heat, when they start performing endurance exercise and/or being exposed to hot conditions on a regular basis. As these individuals continue to be exposed to a given adaptation stimulus, short-term adaptation will follow which is characterized by achieving
a plateau where heat tolerance is significantly elevated. During artificial heat acclimation, this stage is usually achieved within 10–14 days, with ~75-80% of the physiological adaptations evident after 7 days (50, 52). At this point, individuals are considered “low responders” and become quasi resistant to further adaptation. If the active lifestyle in the heat continues, long term heat adaptation can develop; however, this process can take many years to occur.

2.4.3. Natural heat adaptation

Natural heat adaptation, or heat acclimatization, commonly occurs in individuals that reside in very hot climates (e.g., tropics) as well as other regions where heat waves are regularly experienced throughout the year (e.g., Central Canada, north-eastern, mid-western, south-western United States and eastern Europe, Asia, and Africa), albeit seasonal variations in temperatures are often observed (141, 142). If behavioural strategies are minimized (i.e., air conditioning) and physical activity is performed on a regular basis, increases in thermal tolerance will follow. In fact, the physiological adjustments seem to parallel seasonal changes (141, 142). However, Bain et al. (143) recently demonstrated a lack of summer heat acclimatization in young males (~22 years) such that no differences were observed in local heat loss or core temperature responses during a 60-min exercise bout (60% of \( \dot{VO}_{2\text{peak}} \)) in a temperate environment prior to (May) and following (September) a summer in a humid continental climate (i.e. Ottawa, Ontario, Canada). They suggest that modern-day living may be unfavourable for summer heat acclimatization in a humid continental climate due, in part, to the prevalence of air conditioning in houses, vehicles, workplaces and exercise establishments (5). Despite these findings, additional research is warranted to determine if similar responses would be observed in other
demographics such as older adults and individuals with chronic disease (i.e., T2D, cardiovascular disease, etc.).

2.4.4. Artificial heat adaptation

It is well recognized that performing exercise in the heat is the best method to increase the body’s physiological capacity to dissipate heat and lower the level of thermal and cardiovascular strain experienced for a given workload (17, 52). Using a similar incremental intermittent exercise model (three 30-min bouts of cycling at fixed metabolic heat loads of ~300, ~350, and ~400 W·m$^{-2}$) as previously described (6, 7), Poirier et al. (50) demonstrated that 14-days of heat acclimation (90-min of exercise in the heat at 50% of $\dot{V}O_2$peak) can improve the body’s maximal capacity to dissipate heat by as much as 11% in young males (~23 years), with ~75-80% of the total improvements evident after 7 days. Specifically, whole-body evaporative heat loss was increased by 9, 12, and 18% at each heat load, respectively. After taking into account the ~6% in net heat load (due to a 1.6 to 2.1-fold increase in dry heat gain), the relative improvement in evaporative heat loss was ~8, ~8 and ~11%, respectively after 14 days of heat acclimation (i.e., 5, 5, and 9% increase in evaporative heat loss after 7 days, respectively). Altogether, this study demonstrated for the first time that improvements in whole-body evaporative heat loss (and therefore whole-body sweat production) during heat acclimation are heat load-dependent such that they become greater as the heat load increases.

Research examining how older adults physiologically adapt to the heat is limited whereas no studies have evaluated how T2D may alter this response. To date, most studies show that older adults can adapt at the same rate and degree as young adults (91, 107, 140, 144-146), with only two studies reporting a diminished ability to adapt in older adults (11,
103). These contrasting findings may be due to the different experimental designs employed between studies. Foremost, the level of heat acclimation achieved was inconsistent between studies due to differences in the protocols used (i.e., exercise sessions of 30 to 90 min at intensities ranging from 30 to 75% of VO\textsubscript{2peak} for 3 to 14 days). In one particular study, older adults were acclimatized by playing strenuous games in the summer heat 3 times/week for 5-6 weeks while the young adults performed 8 consecutive daily treadmill walks (40 to 90 min of walking at 5.6 km/hour) in the heat (49°C) (103), making it hard to determine whether the “dose” and/or the “intensity” of heat exposure was similar between groups. In addition, all studies to date have employed single heat loads to assess heat acclimation-induced improvements in thermoregulatory capacity. If the chosen heat load did not exceed the individual’s capacity to dissipate heat before heat acclimation, the level of improvement in heat loss may not have been completely detectable thereby contributing to the conflicting findings. Last but not least, most studies have relied on the use of local heat loss responses (sweating and skin blood flow) and core temperatures to determine the effects of heat acclimation on whole-body heat loss and body heat storage. However, local measurements do not always accurately parallel changes occurring from a whole-body perspective (51, 114). Specifically, a recent study demonstrated that increases in local sweat rate (measured on the chest, back and forearm) following 14-days of heat acclimation were not equivalent to the improvements in whole-body sweat rate (51). Moreover, the corresponding decrease in whole-body heat storage was not paralleled by a lower relative change in core temperature (50). Taken together, it remains unclear the extent to which heat acclimation can improve whole-body heat dissipation in older adults and whether the improvements might be altered by the level of heat stress. Furthermore, no
study to date has examined how heat acclimation may alter T2D-related impairments in whole-body heat dissipation (41).

Improvements in sudomotor activity (i.e., reduced onset threshold and increased thermosensitivity of the sweating response), which represent the only mechanism by which we can lose heat in hot conditions (skin temperature < ambient temperature), progressively occur in response to repeated elevations in core temperature (52). However, the magnitude of that improvement is dependent upon each individual’s accommodation “reserve” (i.e., capacity to adapt), which is defined by the individual’s pre-adaptation starting point (i.e., baseline level) and his genetically pre-determined physiological maximum (52). Since it has previously been demonstrated that sedentary older adults with T2D have a lower evaporative heat loss capacity relative to their sedentary non-diabetic counterparts before heat acclimation (i.e., pre-adaptation baseline) (41), there is a possibility that older adults with T2D possess a greater accommodation reserve and therefore a greater capacity to adapt to a given acclimation stimulus. As a result, it is possible that they display a greater enhancement of the sweating response compared to their healthy counterparts during a period of heat acclimation. While this concept is theoretically conceivable, the reverse is also possible, such that adults with T2D may have a compromised ability to physiologically adapt to a given adaptation stimulus relative to adults without T2D due to their general decrease in physiological function (i.e., altered sweat glands and skin vasculature, impaired autonomic and/or cardiovascular function, etc.) related with chronic hyperglycemia (27, 28, 33, 57-59, 119, 122, 123, 130, 132, 135, 138). Nevertheless, there is increasing evidence that aerobic exercise training (i.e., walking, jogging, or cycling) can enhance glycemic control (fasting glycemia and HbA1C) and cardiovascular function, reduce body mass, waist circumference and body adiposity in adults with T2D (24, 42-46), no study to our
knowledge has been explicitly designed to assess how short-term heat acclimation may improve thermoregulatory capacity in adults with T2D. Once it is established at which heat load threshold T2D-mediated impairments in heat dissipation occur, further work is required to determine if heat acclimation can modify this response.
CHAPTER 3

METHODS AND RESULTS
3.1. Thesis article #1

Effects of passive exposure to extreme heat on thermal and cardiovascular strain in habitually active older adults with and without type 2 diabetes

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Word count: 5,985 words

Running Head: Type 2 diabetes and passive heat stress

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ABSTRACT

Aging exacerbates hyperthermia and cardiovascular strain during passive heat exposure, but it remains uncertain whether those effects worsen in older adults with type 2 diabetes. We therefore examined those responses in habitually active, older individuals with (T2D, n=12, mean ± SD age: 60±9 years, HbA1c: 7.0±1.0 %) and without T2D (n=12, 59±4 years) matched for age and physical characteristics during a 3-hour passive exposure to extreme heat (44°C, 30% relative humidity). Metabolic heat production, whole-body net heat loss (dry ± evaporative heat loss), body heat storage (temporal summation of heat production/net heat loss), and rectal temperature were measured continuously, whereas cardiovascular strain (heart rate, cardiac output, mean arterial pressure, and forearm and calf blood flow) was measured before and after the exposure. Metabolic heat production (T2D: 113±18 W; Control: 111±17 W, P=0.70), evaporative heat loss (T2D: 173±32 W; Control: 170±29 W, P=0.94), dry heat exchange (T2D: -98±21 W; Control: -99±28 W P=0.88), and net heat loss (T2D: 75±25 W; Control: 71±22 W, P=0.90) were similar between groups throughout the exposure. Consequently, body heat storage over the 3 hours did not differ significantly between the adults with T2D (344±111 kJ) and without T2D (346±139 kJ, P=0.98). This was paralleled by a similar change in rectal temperature (T2D: 0.4±0.2°C; Control: 0.5±0.3°C, p=0.71). Moreover, the change in forearm and calf blood flow, cardiac output, blood pressure, and heart rate was comparable between groups (all P>0.05). We conclude that habitually active older adults with well-controlled T2D do not experience greater hyperthermia and cardiovascular strain compared to their healthy counterparts during a 3-hour passive exposure to extreme heat.

Keywords: Extreme heat events, heat stress, heat waves, hyperthermia, type 2 diabetes.
INTRODUCTION

Adults above 50 years of age display marked reductions in local heat loss responses (i.e., sweat rate and/or skin blood flow) and/or greater increases core temperature relative to younger individuals during passive heat exposure (1-5), with a recent study reporting age-related impairments in whole-body heat loss that exacerbate increases in body heat storage (6). This maladaptive response may be worse in individuals with chronic medical conditions such as type 2 diabetes (T2D) (7, 8). T2D is associated with higher rates of heat-related illness and death during extreme heat events when compared to the general population (8-10), especially when individuals have longer duration of diabetes (≥5 years), irrespective of medication use (7). This greater risk has been associated to further decreases in skin blood flow (11-15) and sweating (16, 17) measured at single sites across the body (i.e., forehead, forearm, chest, back, thigh, feet and hands). Moreover, studies have shown that adults with T2D have a lower absolute level of cardiovascular function (18) as evidenced by impaired vascular function (11-15), lower increases in cardiac output (19), altered blood pressure regulation (20-22), and reduced autonomic function (23) compared to adults without T2D of the same age. Taken together, these studies have greatly improved our understanding of T2D-mediated impairments in the control of skin blood flow, sweating, and cardiovascular function. However, considerably less is known regarding the combined effect of those reductions in thermoregulatory and cardiovascular function on whole-body heat exchange (evaporative heat loss and dry heat exchange) and the resulting changes in body heat storage and core temperature during heat exposure. This is particularly critical for understanding why older adults with T2D are at increased risk of morbidity and mortality during extreme heat events (8, 9).
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Recently, it was demonstrated that habitually active older adults have a reduced capacity to dissipate heat relative to young adults during a 3-hour passive exposure to extreme heat (44°C and 30% relative humidity), conditions associated with an elevated risk of heat-related morbidity and mortality (24). These age-related impairments in heat dissipation led to greater elevations in body heat storage and core temperature, but similar cardiovascular strain between the older and young adults by the end of the exposure. No study to date, however, has been designed to evaluate whether older adults with T2D experience greater levels of hyperthermia and cardiovascular strain compared to their aged-matched healthy counterparts during the early stages of extreme heat events (i.e., the initial hours of heat exposure). This information is important since epidemiological data demonstrate that adults with T2D are among the most vulnerable during extreme heat events as evidenced by a 56% greater risk for hospitalization and/or mortality (8, 9), especially during the initial hours of the heat wave (25, 26).

The purpose of the present study was therefore to determine if habitually active older adults with well-controlled T2D experience greater levels of hyperthermia and cardiovascular strain during a 3-hour passive exposure to extreme heat conditions (44°C, 30% relative humidity) compared to age-matched healthy adults. We evaluated the hypothesis that adults with T2D would experience greater levels of hyperthermia, as evidenced by a greater change in core temperature, relative to their non-diabetic counterparts. Given that thermometric estimates of body core temperature (i.e., rectal temperature) can sometimes underestimate the level of hyperthermia (27), changes in body heat storage were also assessed as an index of hyperthermia using whole-body direct calorimetry (i.e., a precise method of assessing minute-by-minute changes in whole-body heat loss (dry ± evaporative heat exchange) (28)) and indirect calorimetry (metabolic heat production). We also evaluated the hypothesis that adults with T2D
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would exhibit greater levels of cardiovascular strain compared to adults without T2D by comparing changes in heart rate, stroke volume, cardiac output, mean arterial pressure, and limb blood flow.

METHODS

Ethical approval

The experimental protocol was approved by the University of Ottawa Health Sciences and Science Research Ethics Board and agrees with the Declaration of Helsinki. All volunteers provided written informed consent before participating in the study.

Participants

Twenty-four older (60 ± 7 years) habitually active adults with T2D (n=12) and without T2D (Control, n=12) participated in this study. The participants in the Control group were extracted from the study by Kenny et al. (29) in order to match both groups for age and physical characteristics (Table 1). All participants with T2D had been diagnosed for ≥5 years and were considered generally healthy, had HbA1c of 5.7% to 8.5% (mean of 7.0 ± 1.0%), and no clinically diagnosed T2D-related complications (i.e., peripheral and/or autonomic neuropathy, nephropathy, proliferative retinopathy, unstable cardiac or pulmonary disease). A 3-month recall physical activity questionnaire (30) revealed that all participants were habitually active (i.e., ≥3–4 days per week of continuous exercise of 30–60 min per session).
Experimental Protocol

Participants completed one screening session and one experimental session that involved a 3-hour passive heat exposure inside the Snellen whole-body direct calorimeter in extreme heat (air temperature of 44°C and 30% relative humidity). All trials were performed in the late fall and winter months in Ottawa, Canada. The respective minimum and maximum daily air temperature averaged -18.6 ± 9.1°C and 13.0 ± 9.6°C during the seven-month testing period, with a daily average of -3.0 ± 8.4°C.

During the screening session, body height, mass and density were determined. Body surface area was estimated (31) from measures of body height (Detecto, model 2391, Webb City, MO, USA) and mass (model CBU150X, Mettler Toledo Inc., Mississauga, ON, Canada). Body density was measured using the hydrostatic weighing technique and used to calculate body fat percentage (32).

For the experimental session, participants were asked to abstain from consuming alcohol, caffeine and non-steroidal anti-inflammatory drugs for 24 hours as well as avoid performing strenuous physical activity for 12 hours prior to arriving to the laboratory. They were also instructed to drink ~500 mL of water before going to bed the night before the experimental session as well as upon waking up in the morning to ensure euhydration as no fluids were given during the session. Upon arrival to the laboratory, participants provided a urine sample to allow urine specific gravity to be measured to assess hydration status. Euhydration was defined as a urine specific gravity value below 1.020 (33). Once hydration status was verified, instrumentation occurred in a thermoneutral environment (~26°C) outside the calorimeter while participants remained seated in an upright position (~45 min). Clothing worn during the experiment was limited to a light pair of shorts (females also wore a sports bra) and sandals.
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Baseline thermoregulatory and cardiovascular measurements were taken after the additional ~15 min of rest that followed the instrumentation period. Thereafter, participants were moved to the calorimeter (transition time of ~5 min) where they underwent a 3-hour passive heat exposure while seated in the upright position. At the end of the 3-hour exposure, the final cardiovascular measurements were performed while the participant remained seated inside the calorimeter. We were able to measure cardiac output and limb blood flow only before and after the 3-hour exposure due to the nature of calorimetry requiring an individual to be completely enclosed inside the chamber for the duration to the trial. The ambient conditions for the final cardiovascular measurements were the same as during the heat exposure (i.e., 44°C, 30% relative humidity).

Measurements

The modified Snellen direct air calorimeter was used to directly measure the rates of evaporative and dry heat exchange with an accuracy of ± 2.3 W for the measurement of the rate of net heat loss (28). The calorimeter inflow and outflow values of absolute humidity and air temperature were collected at 8 second intervals. Absolute humidity was measured using high precision dew point hygrometry (RH Systems model 373H, Albuquerque, NM, USA), while air temperature was measured using high precision resistance temperature detectors (±0.002°C, Black Stack model 1560, Hart Electronics, UT, USA). Air mass flow through the calorimeter was measured by differential thermometry over a known heat source (2 x 750 W heating elements) placed in the effluent air stream. The real time data for absolute humidity, air temperature, and air mass flow was displayed and recorded on a personal computer with LabVIEW software (Version 7.0, National Instruments, Austin, TX, USA). The rate of
evaporative heat loss was calculated using the calorimeter outflow–inflow difference in absolute humidity, multiplied by the air mass flow (kg air∙s⁻¹) and the latent heat of vaporization of sweat (2,426 J·g sweat⁻¹). The rate of dry heat exchange was calculated using the calorimeter outflow–inflow difference in air temperature, multiplied by the air mass flow and specific heat capacity of air (1,005 J·kg air⁻¹∙°C⁻¹). Indirect calorimetry was used for the simultaneous measurement of metabolic energy expenditure (27). The temporal summation of whole-body heat loss (combined evaporative heat loss and dry heat exchange) and metabolic heat production was used to calculate body heat storage (27).

Rectal temperature was measured continuously using a thermocouple probe (Mon-a-therm General Purpose Temperature Probe, Mallinckrodt Medical, St-Louis, MO, USA) inserted to a minimum of 12 cm past the anal sphincter. Skin temperature was measured at four locations (i.e., upper back, chest, thigh, and calf) over the left side of the body using 0.3-mm-diameter T-type (copper/constantan) thermocouples (Concept Engineering, Old Saybrook, CT) affixed to the skin with surgical tape. Mean skin temperature was calculated using 4 skin temperatures weighted to the regional proportions proposed by Ramanathan: chest 30%, biceps 30%, thigh 20%, and calf 20% (34). Rectal and skin temperature data were collected using an HP Agilent data acquisition module (model 3497A; Agilent Technologies Canada Inc., Mississauga, ON, Canada) at a rate of one sample every 15 s and simultaneously displayed and recorded in spreadsheet format on a personal computer with LabVIEW software (Version 7.0, National Instruments, Austin, TX).

Local sweat rate was measured on the thigh, chest, upper back, and forearm using 2.8 cm² ventilated capsules. The sweat capsules were attached to the skin with adhesive rings and topical skin glue (Collodion HV, Mavidon Medical products, Lake Worth, FL, USA). Dry compressed
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air was supplied to each capsule at a rate of 1.0 L•min\(^{-1}\), while water content of the effluent air was measured with capacitance hygrometers (Model HMT333, Vaisala, Helsinki, Finland). Local sweat rate was calculated using the difference in water content between effluent and influent air multiplied by the flow rate and normalised for the skin surface area under the capsule.

Heart rate was recorded continuously and stored every 5 sec using a Polar coded WearLink and transmitter, Polar RS400 interface and Polar Trainer 5 software (Polar Electro, Kempele, Finland).

The physiological strain index was calculated from the measurements of rectal temperature and heart rate using the following equation (35):

\[
\text{Physiological strain index} = 5 \cdot \frac{T_{\text{ret}} - T_{\text{rebl}}}{39.5 - T_{\text{rebl}}} + 5 \cdot \frac{HR_t - HR_{bl}}{HR_{\text{max}} - HR_{bl}}
\]

where \(T_{\text{ret}}\) is the rectal temperature recorded at a given time point (°C), \(T_{\text{rebl}}\) is the rectal temperature recorded at baseline (°C), \(HR_t\) is the heart rate recorded at a given time point (beats min\(^{-1}\)), and \(HR_{bl}\) is the heart rate recorded at baseline (beats min\(^{-1}\)), and \(HR_{\text{max}}\) is the age predicted maximal heart rate (beats min\(^{-1}\)). Thermal sensation was also assessed every 30-min using the ASHRAE 7-point scale (0 = Neutral to 7 = Very, Very Hot).

Prior to and following a 3-hour heat exposure, cardiovascular responses were measured inside the direct calorimeter. Specifically, we assessed: [1] resting heart rate (RS400, Polar, Kempele, Finland); [2] cardiac output via the inert gas (mixture consisting of 5% blood soluble \(N_2O\), 1% blood insoluble \(SF_6\), and 94% of \(O_2\)) rebreathing technique as established by Innocor (Innovision, Odense, Denmark); [3] arterial blood pressure via manual auscultation with a validated mercury sphygmomanometer (Baumanometer Standby Model, WA Baum Co, Copiague, NY, USA); and [4] limb blood flow (forearm and calf) by venous occlusion
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plethysmography (Hokanson AI6, D.E. Hokanson, Inc., Bellevue, WA, USA). Stroke volume was calculated as cardiac output/heart rate, while total peripheral resistance was calculated as mean arterial pressure/cardiac output.

**Statistical Analysis**

An *a priori* power analysis was performed using the observed difference in the primary variable of interest (cumulative body heat storage) during the same extreme heat exposure between young and older adults in our previous work (6). Based on the effect size (Cohen’s $d = 1.12$) for a 156 kJ difference in body heat storage between groups with a pooled standard deviation of 139 kJ (6), a minimum of eleven subjects were required to detect between-group differences of this effect size with at least 80% statistical power (36). Therefore, with the current sample ($n=12$), these analyses were adequately powered (>80%). The dependent variables for whole-body calorimetry (i.e., metabolic heat production, net heat loss, evaporative heat loss, and dry heat exchange), local thermoregulatory responses (i.e., rectal and mean skin temperatures, local sweat rates, and physiological strain index) and thermal sensation were analyzed using a repeated-measures analysis of variance to assess between-group (2 levels: T2D and Control) differences throughout (6 levels: minutes 0-30, 31-60, 61-90, 91-120, 121-150, and 151-180) the 3-hour passive heat exposure. The same analysis was used to compare pre- and post-cardiovascular responses in the two groups. In cases where a main effect was detected, post-hoc comparisons were carried out using paired (time) or unpaired (group) *t* tests. For comparisons between time points, the *P* value was adjusted with the Bonferroni procedure as a multiple comparison. Furthermore, unpaired *t* tests were used for between-group comparisons of participant characteristics. For all analyses, *Alpha* was set at the 0.05 level. Data are reported as
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means (SD). All statistical analyses were conducted using SPSS 25 (IBM, Armonk, NY, USA) statistical software.

RESULTS

Participant characteristics and urine specific gravity

No between-group differences were evident for age, height, body mass, body mass index, fat percentage, and surface area (all P>0.05). All participants were similarly euhydrated as indicated by baseline urine specific gravity (T2D: 1.018 ± 0.008; Control: 1.017 ± 0.008, P=0.818).

Whole-body heat exchange

Metabolic heat production increased over time (P<0.01) with no difference detected between groups (P=0.701) (Table 2). While dry heat exchange decreased across the exposure (P<0.01), evaporative heat loss increased over time (P<0.01). However, no significant differences in dry heat exchange or evaporative heat loss were observed between groups throughout the 3-hour exposure (both P>0.05, Table 2). As a result, net heat loss increased over time (P<0.01), with a comparable response measured between the adults with and without T2D (P=0.90). The change in body heat storage decreased over time (P<0.01) with no between-group differences observed throughout the exposure (P=0.85, Figure 1). Similarly, the cumulative amount of heat stored over the 3 hours of exposure was also comparable between both groups (P=0.98, Figure 1).
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**Tissue temperatures, local heat loss responses, physiological strain index, and thermal sensation**

Rectal and mean skin temperatures increased over time (both P<0.01), albeit the response was similar between groups (both P>0.05, Table 3). While local sweat rate on the chest (P<0.01) and forearm (P=0.02) increased throughout the heat exposure in both groups, no increase was observed on the thigh (P=0.49) and back (P=0.45) (Table 3). No between-group differences were measured in local sweat rate at all four sites over the 3-hour exposure (all P>0.05). Moreover, thermal sensation and physiological strain index both increased across time (both p<0.001), although no differences were measured between groups (both P>0.05, Table 3).

**Cardiovascular responses**

Heart rate, forearm blood flow, and calf blood flow increased as a function of time in both groups (all p<0.01, Table 4). Mean arterial pressure, total peripheral resistance and cardiac output remained unaffected (all P>0.05), while stroke volume decreased over time (P<0.01). No between-groups differences in heart rate, forearm and calf blood flow, mean arterial pressure, total peripheral resistance, cardiac output and stroke volume were observed at baseline or at the end of the 3-hour heat exposure (all P>0.05, Table 4).

**DISCUSSION**

In contrast to our working hypotheses, habitually active older adults with well-controlled T2D did not experience greater levels of hyperthermia or cardiovascular strain compared to their age-matched healthy counterparts during a 3-hour passive exposure to extreme heat. This was evidenced by similar whole-body net heat loss between groups, which led to comparable body
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heat storage and similar increases in rectal temperature between groups. Further, similar changes in forearm and calf blood flow, mean arterial pressure, total peripheral resistance, cardiac output and stroke volume were observed between groups. Taken together, these outcomes indicate that T2D does not worsen the effects of extreme heat exposure on thermoregulatory and cardiovascular function in older, habitually active adults.

A recent study demonstrated that habitually active older adults display a reduced capacity to dissipate heat and greater body heat storage compared to young adults (18-30 years) during a short 3-hour passive exposure (44ºC and 30% relative humidity) (6). These age-related impairments in whole-body heat dissipation and heat storage were expected to be exacerbated in older adults with T2D as these individuals typically demonstrate further reductions in skin blood flow (11-15) and sweating (16, 17) as well as a greater risk of heat-related morbidity and mortality during extreme heat events relative to their age-matched healthy counterparts (8, 9). However, contrary to that hypothesis, T2D did not further impair whole-body evaporative heat loss and dry heat exchange, and therefore whole-body net heat loss, during a short 3-hour passive exposure to extreme heat relative to healthy non-diabetic older adults (Table 2). As a result, both groups stored the same amount of heat throughout the duration of the exposure (Figure 1). These findings were paralleled by similar changes in local sweat rate (thigh, chest, upper back, and mid-anterior forearm), rectal and mean skin temperatures, heart rate, physiological strain index, and thermal sensation throughout the 3-hour exposure (Tables 3 and 4). These outcomes demonstrate that the risk of heat-related injury and death in the initial hours of extreme heat exposure is comparable between habitually active older adults with and without T2D.

Contrary to our working hypothesis, we found that T2D did not further compromise the cardiovascular adjustments that occurred during the 3-hour exposure (Table 4). This lack of
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difference is surprising given that T2D has been associated with reductions in baroreflex sensitivity (20, 22) and sympathetic neural control of blood pressure (21), impaired cerebral blood flow (37) and vascular function (11-15), diminished increase in cardiac output (19), as well as reduced heart rate variability (i.e., indicator of autonomic function) (23) relative to age-matched healthy controls. However, an important consideration of the current study is that the level of hyperthermia experienced was modest (i.e., rectal temperature increase of ~0.4-0.5ºC) and of similar magnitude in both groups. Therefore, we cannot discount the possibility that differences in cardiovascular strain may have transpired if the level of hyperthermia was greater as a result of a greater thermal load imposed by the environment (i.e., increase in air temperature and/or solar load – which was not present in the current study) and/or during a more prolonged exposure. Furthermore, it is important to note that the cardiovascular adjustments measured in the individuals with T2D were considered acceptable for the degree of heat stress employed as they did not markedly differ from those observed in young adults who underwent the same 3-hour extreme heat exposure (29). However, both groups in this study exhibited a ~13% reduction in limb perfusion compared to the young adults (29). This decreased limb perfusion could worsen over time and contribute to the exacerbated risk of cardiovascular-related morbidity and mortality in older adults with and without T2D during heat waves (8-10, 38).

The similar pattern of response in whole-body heat loss as well as the lack of discernable differences in thermal and cardiovascular strain between groups may be due to the fact that the T2D patients were as habitually active as those without T2D (~7.0 and ~7.5 hours of light to moderate intensity physical activity per week in both groups, respectively). While this active lifestyle might have helped maintain a greater capacity to dissipate heat (39), aerobic capacity was not measured therefore it is difficult to compare the aerobic fitness levels of both groups.
Type 2 diabetes and passive heat stress

Furthermore, the adults with T2D in this study were normotensive, free of diabetes-related complications (i.e., renal disease, peripheral and/or autonomic neuropathy, unstable cardiac/pulmonary disease, and other micro- and macrovascular complications), and had good glycemic control (HbA1c of 7.0%). Several studies have shown that eccrine sweat glands can be altered by neuropathy and poor glucose control (i.e., lower number of innervated sweat glands) (17, 40, 41), thus reducing sweat gland output (primarily due to reduced lower body sweating and possible anhydrosis (17)) and attenuating the potential for sweat evaporation. Additionally, greater impairments in skin blood flow (i.e., lower maximal response) and cardiovascular function have also been associated with poor glucose control and neuropathy (7, 17, 23, 41-43). Further investigations are therefore required to determine how the additive effects of these factors may alter whole-body evaporative heat loss and dry heat exchange and the resulting changes in thermal and cardiovascular strain during passive exposure to extreme heat.

In contrast to our findings, a recent study (44) reported that older adults with T2D (~56 years, hemoglobin A1c of 7.3%) have a lower whole-body evaporative heat loss (and therefore whole-body sweat production) response during a 60-min continuous exercise bout (metabolic heat production of ~370 W) in a warm environment (30˚C) compared to adults without T2D, leading to a 35% greater body heat storage in the T2D group. The disparity between studies may be due to the fact that the heat load imposed by exercise may have been great enough to distinguish T2D-related impairments in whole-body heat loss. This has been demonstrated for various other intrinsic factors such as age (39, 45), sex (46), aerobic fitness (47) such that impairments and/or improvements in heat dissipation only become evident above a specific heat load threshold (as defined by the combined metabolic and environmental heat loads), with the magnitude of difference typically becoming greater with increases in heat load. Future studies
Type 2 diabetes and passive heat stress are therefore warranted to determine the exact heat stress threshold at which T2D begins to impair the body’s capacity to dissipate heat.

**Perspective**

Our study provides important new insights into the effects of T2D on the body’s capacity to dissipate heat during passive heat exposure. Our findings have important implications for heat advisories during heat waves as well for defining heat exposure limits. Specifically, habitually active older adults with well-controlled T2D can now be considered within the same population group as their habitually active healthy counterparts due to the similar thermal (body heat storage and core temperature responses) and cardiovascular strain experienced during the early hours of a heat wave. However, it remains unclear whether this similar pattern of response would remain intact for an extended exposure period (>3 hours). This is particularly important since both groups in the current study were unable to achieve heat balance (heat gain matched by heat loss) by the end of the 3 hours of exposure, averaging a rate of body heat storage of 13 ± 6 W in the last hour. If this rate of body heat storage was sustained, core body temperature could exceed 39°C in both groups after an 8-hour exposure. In comparison, the projected increase in young adults over the same time frame would be ~50% lower in comparison to older adults with and without T2D (29). Altogether, the small differences in heat dissipation could lead to high levels of hyperthermia over a prolonged period of time, especially in older adults with and without T2D. However, to avoid such situations from occurring, it is essential that everyone take the steps necessary (e.g. use of air conditioners, fans, cold-water showers, etc.) to reduce exposure to extreme heat in order to mitigate their risk of heat-related morbidity and mortality, especially considering that heat waves can last 3 days or more (48, 49).
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Furthermore, it remains unclear whether older adults with T2D may experience greater levels of hyperthermia and cardiovascular strain during more humid passive heat exposure. In such conditions, heat exchange efficiency is impaired as the rate of sweat evaporation is gradually reduced with increasing levels of humidity (50). Therefore, profuse sweating with no evaporation will not contribute to heat loss but rather to a quicker state of dehydration, which could then lead to reductions in skin blood flow and skin temperatures, and potentially increase the rate of dry heat gain. Based on the greater impairments in skin blood flow and cardiovascular function in adults with T2D (11-15, 19-23, 37), additional studies are needed to determine whether T2D may alter whole-body evaporative heat loss and dry heat exchange and the subsequent changes in the level of hyperthermia and cardiovascular strain during passive exposure to humid heat. While research examining the effects of T2D on thermoregulatory function remains a relatively new area of investigation, such knowledge will help facilitate the development of guidelines and policies related to the management of vulnerable populations in extreme heat conditions. This is time-sensitive given that the frequency and severity of extreme heat events is projected to increase considerably in coming years (51, 52), which is paralleled by an aging population and an increase in the incidence and prevalence of T2D (53).

CONCLUSIONS

We showed that habitually active older adults with well-controlled T2D and free of any known T2D-related complications and other health conditions do not experience greater levels of thermal and cardiovascular strain during a short 3-hour extreme heat exposure compared to adults without T2D. While our observations over 3 hours were not clinically alarming, the inability to achieve a sufficiently elevated rate of heat dissipation to achieve heat balance (and
Type 2 diabetes and passive heat stress

therefore a stable core temperature) could potentially lead to dangerous levels of hyperthermia and cardiovascular strain during more prolonged exposures, which is critical considering that heat waves can extend over multiple days. We suggest that adults with and without T2D be cautious and undertake appropriate preventive measures (i.e., move to shaded and/or cooler areas, air conditioners, fans, cold water immersion, etc.) during exposure to extreme heat to reduce the likelihood of heat-related injury and/or death.

ACKNOWLEDGMENTS

The authors are indebted to the study participants and to Ms. Joanie Larose for her invaluable help with data collection. The authors would also like to thank all members of the Human and Environmental Physiology Research Unit.

GRANTS

The study was conducted at the Human and Environmental Physiology Research Unit (HEPRU). This study was funded by the Canadian Institutes of Health Research (Grant number 286363, held by G. P. Kenny). G. P. Kenny was supported by a University of Ottawa Research Chair Award. M. P. Poirier was supported by Natural Sciences and Engineering Research Council of Canada Alexander Graham Bell Scholarship (CGS-D), HEPRU, as well as the University of Ottawa. S.R. Notley was supported by a Postdoctoral Fellowship from HEPRU. B. J. Friesen was supported by an Ontario Graduate Scholarship. R.J. Sigal was supported by a Health Senior Scholar award from Alberta Innovates-Health Solutions.
AUTHOR CONTRIBUTIONS

All authors conceptualized and designed the research. M.P.P. performed experiments. M.P.P. performed data analysis. All authors interpreted the experimental results. M.P.P. prepared figures and drafted manuscript. All authors edited and revised the manuscript. All authors approved the final version of the manuscript.
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REFERENCES


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Table 1. Participant characteristics.

<table>
<thead>
<tr>
<th></th>
<th>T2D (n=12)</th>
<th>Control (n=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males (#)</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Females (#)</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Age (years)</td>
<td>60 ± 9</td>
<td>59 ± 4</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.74 ± 0.06</td>
<td>1.76 ± 0.07</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>89.9 ± 16.0</td>
<td>84.7 ± 11.1</td>
</tr>
<tr>
<td>Body mass index (kg·m$^{-2}$)</td>
<td>29.6 ± 5.1</td>
<td>27.5 ± 3.5</td>
</tr>
<tr>
<td>Body fat (%)</td>
<td>30.6 ± 6.9</td>
<td>27.6 ± 9.1</td>
</tr>
<tr>
<td>Body surface area (m$^2$)</td>
<td>2.1 ± 0.2</td>
<td>2.0 ± 0.1</td>
</tr>
<tr>
<td>Hemoglobin A1c (%)</td>
<td>7.0 ± 1.0</td>
<td>----</td>
</tr>
<tr>
<td>Duration of diabetes (years)</td>
<td>12 ± 5</td>
<td>----</td>
</tr>
</tbody>
</table>

Values are mean ± SD. There were no significant differences between groups, P>0.05.
Table 2. Whole-body calorimetry data during the 3-hour passive heat exposure in adults with T2D and without T2D (Control).

<table>
<thead>
<tr>
<th>Group</th>
<th>Time (min)</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0-30</td>
<td>31-60</td>
<td>61-90</td>
<td>91-120</td>
<td>121-150</td>
</tr>
<tr>
<td>Metabolic heat production, W</td>
<td>T2D</td>
<td>106 ± 17</td>
<td>108 ± 16</td>
<td>110 ± 16</td>
<td>113 ± 17</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>108 ± 14</td>
<td>110 ± 15</td>
<td>111 ± 15</td>
<td>113 ± 16</td>
</tr>
<tr>
<td>Net heat loss, W</td>
<td>T2D</td>
<td>28 ± 23</td>
<td>61 ± 14</td>
<td>82 ± 18</td>
<td>96 ± 18</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>31 ± 26</td>
<td>65 ± 27</td>
<td>88 ± 21</td>
<td>98 ± 16</td>
</tr>
<tr>
<td>Evaporative heat loss, W</td>
<td>T2D</td>
<td>147 ± 32</td>
<td>168 ± 24</td>
<td>179 ± 29</td>
<td>186 ± 30</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>148 ± 25</td>
<td>168 ± 27</td>
<td>182 ± 28</td>
<td>187 ± 26</td>
</tr>
<tr>
<td>Dry heat exchange, W</td>
<td>T2D</td>
<td>-119 ± 29</td>
<td>-106 ± 27</td>
<td>-97 ± 26</td>
<td>-90 ± 24</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>-117 ± 21</td>
<td>-102 ± 17</td>
<td>-94 ± 19</td>
<td>-90 ± 20</td>
</tr>
</tbody>
</table>

Values are mean ± SD. Net heat loss is defined as the combined rates of evaporative heat loss and dry heat exchange. The negative values for dry heat exchange represent dry heat gain. There were no significant differences between groups, P>0.05.
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**Table 3.** Rectal and mean skin temperatures, local sweat rates, physiological strain, and subjective thermal sensation during the 3-hour passive heat exposure in adults with T2D and without T2D (Control).

<table>
<thead>
<tr>
<th>Group</th>
<th>Time (min)</th>
<th>Rectal temperature (°C)</th>
<th>Mean skin temperature (°C)</th>
<th>Forearm sweat rate (mg·min⁻¹·cm⁻²)</th>
<th>Upper back sweat rate (mg·min⁻¹·cm⁻²)</th>
<th>Chest sweat rate (mg·min⁻¹·cm⁻²)</th>
<th>Thigh sweat rate (mg·min⁻¹·cm⁻²)</th>
<th>Thermal sensation (°C)</th>
<th>Physiological strain</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0-30</td>
<td>31-60</td>
<td>61-90</td>
<td>91-120</td>
<td>121-150</td>
<td>151-180</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rectal</td>
<td>T2D</td>
<td>37.4 ± 0.4</td>
<td>37.5 ± 0.3</td>
<td>37.6 ± 0.3</td>
<td>37.7 ± 0.3</td>
<td>37.8 ± 0.2</td>
<td>37.8 ± 0.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>37.3 ± 0.2</td>
<td>37.4 ± 0.2</td>
<td>37.6 ± 0.2</td>
<td>37.6 ± 0.2</td>
<td>37.7 ± 0.2</td>
<td>37.7 ± 0.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean skin</td>
<td>T2D</td>
<td>35.9 ± 0.4</td>
<td>36.1 ± 0.4</td>
<td>36.2 ± 0.4</td>
<td>36.2 ± 0.4</td>
<td>36.3 ± 0.4</td>
<td>36.4 ± 0.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>35.9 ± 0.4</td>
<td>36.0 ± 0.4</td>
<td>36.1 ± 0.4</td>
<td>36.1 ± 0.4</td>
<td>36.1 ± 0.4</td>
<td>36.2 ± 0.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Forearm</td>
<td>T2D</td>
<td>0.65 ± 0.17</td>
<td>0.68 ± 0.21</td>
<td>0.69 ± 0.26</td>
<td>0.67 ± 0.21</td>
<td>0.67 ± 0.23</td>
<td>0.67 ± 0.22</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>0.62 ± 0.18</td>
<td>0.65 ± 0.20</td>
<td>0.68 ± 0.20</td>
<td>0.71 ± 0.22</td>
<td>0.72 ± 0.22</td>
<td>0.71 ± 0.22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper back</td>
<td>T2D</td>
<td>0.73 ± 0.24</td>
<td>0.75 ± 0.27</td>
<td>0.77 ± 0.33</td>
<td>0.77 ± 0.28</td>
<td>0.80 ± 0.28</td>
<td>0.83 ± 0.33</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>0.63 ± 0.22</td>
<td>0.65 ± 0.18</td>
<td>0.66 ± 0.20</td>
<td>0.68 ± 0.21</td>
<td>0.71 ± 0.26</td>
<td>0.70 ± 0.27</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chest</td>
<td>T2D</td>
<td>0.53 ± 0.17</td>
<td>0.52 ± 0.16</td>
<td>0.52 ± 0.16</td>
<td>0.53 ± 0.17</td>
<td>0.55 ± 0.17</td>
<td>0.56 ± 0.17</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>0.57 ± 0.17</td>
<td>0.60 ± 0.19</td>
<td>0.62 ± 0.19</td>
<td>0.65 ± 0.19</td>
<td>0.67 ± 0.18</td>
<td>0.67 ± 0.18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thigh</td>
<td>T2D</td>
<td>0.54 ± 0.12</td>
<td>0.54 ± 0.19</td>
<td>0.54 ± 0.21</td>
<td>0.54 ± 0.21</td>
<td>0.55 ± 0.22</td>
<td>0.57 ± 0.25</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>0.51 ± 0.15</td>
<td>0.51 ± 0.14</td>
<td>0.51 ± 0.16</td>
<td>0.52 ± 0.16</td>
<td>0.53 ± 0.16</td>
<td>0.53 ± 0.15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thermal</td>
<td>T2D</td>
<td>3.3 ± 0.8</td>
<td>3.5 ± 1.0</td>
<td>3.8 ± 1.1</td>
<td>4.1 ± 1.4</td>
<td>4.2 ± 1.4</td>
<td>4.2 ± 1.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>2.9 ± 1.6</td>
<td>3.2 ± 1.3</td>
<td>3.5 ± 1.5</td>
<td>3.9 ± 1.8</td>
<td>3.9 ± 2.1</td>
<td>4.0 ± 2.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physiological</td>
<td>T2D</td>
<td>0.05 ± 0.18</td>
<td>0.37 ± 0.49</td>
<td>0.77 ± 0.49</td>
<td>1.31 ± 0.52</td>
<td>1.75 ± 0.86</td>
<td>2.09 ± 1.06</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>0.11 ± 0.14</td>
<td>0.65 ± 0.43</td>
<td>1.10 ± 0.69</td>
<td>1.53 ± 0.80</td>
<td>1.71 ± 0.90</td>
<td>1.93 ± 0.93</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are mean ± SD. There were no significant differences between groups, P>0.05.
Table 4. Cardiovascular responses at baseline and at the end of the 3-hour passive heat exposure in adults with T2D and without T2D (Control).

<table>
<thead>
<tr>
<th></th>
<th>Group</th>
<th>Baseline</th>
<th>Post</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Resting heart rate</strong></td>
<td>T2D</td>
<td>82 ± 14</td>
<td>101 ± 17*</td>
</tr>
<tr>
<td>(beats min⁻¹)</td>
<td>Control</td>
<td>73 ± 1</td>
<td>89 ± 14*</td>
</tr>
<tr>
<td><strong>Cardiac output</strong></td>
<td>T2D</td>
<td>4.5 ± 1.0</td>
<td>4.6 ± 0.9</td>
</tr>
<tr>
<td>(L·min⁻¹)</td>
<td>Control</td>
<td>4.6 ± 1.2</td>
<td>4.2 ± 1.1</td>
</tr>
<tr>
<td><strong>Stroke volume</strong></td>
<td>T2D</td>
<td>56 ± 19</td>
<td>47 ± 9*</td>
</tr>
<tr>
<td>(ml)</td>
<td>Control</td>
<td>63 ± 16</td>
<td>49 ± 15*</td>
</tr>
<tr>
<td><strong>Mean arterial pressure</strong></td>
<td>T2D</td>
<td>96 ± 8</td>
<td>96 ± 7</td>
</tr>
<tr>
<td>(mmHg)</td>
<td>Control</td>
<td>93 ± 6</td>
<td>95 ± 11</td>
</tr>
<tr>
<td><strong>Total peripheral resistance</strong></td>
<td>T2D</td>
<td>21 ± 7</td>
<td>22 ± 4</td>
</tr>
<tr>
<td>(mmHg· L·min⁻¹)</td>
<td>Control</td>
<td>22 ± 7</td>
<td>23 ± 13</td>
</tr>
<tr>
<td><strong>Forearm blood flow</strong></td>
<td>T2D</td>
<td>2.5 ± 0.7</td>
<td>4.0 ± 2.1*</td>
</tr>
<tr>
<td>(ml·100 ml tissue⁻¹·min⁻¹)</td>
<td>Control</td>
<td>2.7 ± 0.9</td>
<td>4.9 ± 1.8*</td>
</tr>
<tr>
<td><strong>Calf blood flow</strong></td>
<td>T2D</td>
<td>1.7 ± 0.4</td>
<td>3.0 ± 0.8*</td>
</tr>
<tr>
<td>(ml·100 ml tissue⁻¹·min⁻¹)</td>
<td>Control</td>
<td>1.6 ± 0.6</td>
<td>3.0 ± 1.4*</td>
</tr>
</tbody>
</table>

Values are mean ± SD. (*) Significantly different from baseline, P<0.05.
**Figure 1.** The mean change in body heat storage for each 30-min period as well as the cumulative change throughout 3-hours of passive heat exposure in adults with T2D and without T2D (Control). Body heat storage was calculated as the temporal summation of metabolic heat production and net heat loss. Values are mean ± SD. There were no significant differences between groups, P>0.05.
3.2. Thesis article #2

Type 2 diabetes impairs whole-body heat dissipation in a heat load-dependent manner in habitually active older males

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Word count: 6,824 words

Running Head: Type 2 diabetes and exercise heat stress

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Type 2 diabetes and exercise heat stress

ABSTRACT

Sedentary individuals with type 2 diabetes (T2D) display impaired heat dissipation at rest and during exercise in the heat, placing them at greater risk for heat-related illness. However, it remains unclear if this dysfunction exists in habitually active adults or whether those impairments worsen with increasing levels of heat stress. We therefore assessed changes in whole-body heat loss in habitually active older males (59±5 years) with (n=16, HbA1c: 6.8±1.0%) and without (Control, n=16) well-controlled T2D matched for age and peak aerobic power (VO_{2peak}). Participants completed three 30-min cycling bouts at increasing exercise-induced heat loads (and therefore level of heat stress) of 150 (low), 200 (moderate), 250 (high) W m^{-2} (equal to ~36, ~49, and ~61% of VO_{2peak}), each followed by 15-min recovery, in dry-heat (40°C, ~15% relative humidity). Whole-body heat exchange (evaporative ± dry) and metabolic heat production were measured using direct and indirect calorimetry, respectively. Body heat storage was quantified as the temporal summation of heat production and loss. Dry heat gain was similar across exercise bouts and between groups (both P>0.05), averaging -48±14 W m^{-2}. However, evaporative heat loss was reduced for T2D relative to Control during moderate (211±26 vs. 229±23 W m^{-2}, P=0.04) and high (234±36 vs. 261±30 W m^{-2}, P=0.03) heat loads. Consequently, body heat storage over the three exercise bouts was 27% greater in T2D (651±204 kJ) compared to Control (476±157 kJ, P=0.01). We conclude that T2D impairs whole-body evaporative heat loss and exacerbates heat storage in habitually active older males with well-controlled T2D at moderate-to-high (≥200 W m^{-2}) exercise-induced heat loads.

Keywords: Aging, core temperature, diabetes, exercise, heat stress, hyperthermia, sweating.
INTRODUCTION

Aging causes marked reductions in the body’s capacity to dissipate heat during rest and exercise in hot environments (primarily via reductions in the evaporation of sweat), which exacerbate body heat storage in adults as young as 40 years of age (1-7). A recent topical review revealed that age-related deteriorations in thermoregulatory function may be worse in individual with type 2 diabetes (T2D) (8). This is supported by epidemiological data demonstrating that older adults with T2D are at greater risk of hospitalization and/or death during hot environmental conditions when compared to the general population (9-11). Importantly, this risk is exacerbated among individuals with longer duration of diabetes (≥5 years), and exists regardless of medication use (8). However, this maladaptive response has been ascribed to reductions in skin blood flow (12-18) and sweat production (19-21), albeit measured at single body regions on the torso, limbs and extremities. Evaluations of whether those local reductions in effector function translate into meaningful decrements in global (whole-body) changes in the body’s ability to lose heat during exercise-induced heat stress are sparse (22).

Indeed, to our knowledge, only one study to date has evaluated how T2D-related reductions in skin blood flow and sweating may translate into impairments in whole-body heat exchange (22). Using direct calorimetry, which is a gold standard method to assess time-dependent changes in whole-body dry and evaporative heat exchange and the resulting alterations in body heat storage, sedentary older (58 years) adults with and without T2D were evaluated during a single bout of light-to-moderate intensity exercise (60 min) in a warm environment (30°C). The adults with T2D displayed reductions in whole-body evaporative heat loss (and therefore whole-body sweating) that caused nearly 1.6-times more body heat storage relative to their healthy counterparts. However, it is known that good glycemic control and maintenance of aerobic fitness can often delay the T2D-mediated complications and possibly the impairments in heat loss. In support of this possibility, habitually active older adults with higher aerobic
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fitness (as defined by peak aerobic power ($\bar{VO}_{2\text{peak}}$)) possess greater heat loss capacity relative to their sedentary counterparts, which can attenuate age-related impairments in thermoregulatory function (4). This is fundamentally important, as exercise is a cornerstone in T2D management due to its ability to improve glycemic control and aerobic fitness (23). However, this response is only evident above a certain level of heat stress (as defined by net heat gained from the environment and/or exercise). Indeed, it is well established that multiple individual factors (e.g., aerobic fitness, sex, aging, others) modulate heat exchange to a greater extent at higher exercise-induced heat loads (3, 4, 24-26). As such, it is possible that any impairments in whole-body heat dissipation among habitually active older adults with T2D may worsen as a function of the exercise-induced heat load, and therefore level of heat stress, increasing the risk of heat-related injury (or death) when performing physical activity, especially in the heat and/or at higher exercise intensities. This is conceivable since adults with T2D have been shown to have a blunted increase in maximal skin blood flow and sweating compared to adults without T2D during progressive increases in environmental heat load (~22 to 42°C) (14, 20), albeit these observations occurred under resting conditions. Furthermore, our previous examination of whole-body heat exchange in sedentary adults with T2D was also limited to a single exercise bout (22).

The purpose of this study was therefore to assess time-dependent changes in whole-body dry and evaporative heat exchange in habitually active older adults with and without T2D during elevations in the level of heat stress associated with increases in heat load generated by exercise (increases in metabolic rate augments the rate at which heat must be dissipated). Given that T2D-mediated impairments in whole-body heat loss were solely due to a reduced evaporative heat loss in our previous study (22), we hypothesized that habitually active older men with T2D would exhibit lower whole-body evaporative heat loss, albeit this response would be heat load-dependent such that impairments would worsen with increases in exercise-induced heat load (22). The knowledge acquired from this study will
Type 2 diabetes and exercise heat stress vastly improve our understanding of the effects of T2D on the body’s physiological capacity to dissipate heat and aid our ability to manage heat stress among habitually active older men engaged in physical activity.

MATERIALS AND METHODS

Ethical approval

The experimental protocol was approved by the University of Ottawa Health Sciences and Science Research Ethics Board and conforms to the Declaration of Helsinki. All volunteers provided written, informed consent before participating in the study.

Participants

Thirty-two habitually active older males with (T2D, n=16) or without Control, n=16) T2D participated in this study (Table 1). Participants were selected based on their age, physical characteristics and VO2peak to minimize between-group differences in age, body surface area, and aerobic fitness. All participants with T2D had been diagnosed for ≥5 years and were considered generally healthy, had an HbA1c of 5.5% to 8.5% (mean of 6.8 ± 0.9%), and no clinically diagnosed T2D-related complications (i.e., peripheral and/or autonomic neuropathy, nephropathy, proliferative retinopathy, unstable cardiac or pulmonary disease). A 3-month recall physical activity questionnaire (27) revealed that all participants were habitually active (i.e., ≥3–4 days per week of continuous exercise of 30–60 min per session), which are in line with the recommendations set forth by Diabetes Canada (23).
Experimental Protocol

Participants underwent one screening and one experimental session. During the screening session, body height was measured using a stadiometer (Detecto, model 2391, Webb City, MO, USA), while body mass was measured using a digital high-performance weighing terminal (model CBU150X, Mettler Toledo Inc., Mississauga, ON, Canada). From these measures, body surface area was calculated (28). Body density was measured using the hydrostatic weighing technique and used to estimate body fat percentage (29). All participants performed an incremental maximal exercise test (30) on a semi-recumbent cycle ergometer (Corival, Lode B. V., Groningen, Netherlands) to determine \( \dot{V}O_2 \)peak (MCD Medgraphics Ultima Series, MGC Diagnostics, MN, USA). For all healthy males above 55 years of age as well as all participants with T2D, a 12-lead electrocardiogram was performed during the exercise test to detect any cardiac abnormalities. Individuals with cardiac abnormalities were not permitted to participate.

For the experimental session, participants were asked to refrain from consuming alcohol, caffeine, and over-the-counter medications for 24 hours prior to experimentation, and to avoid major thermal stimuli on their way to the laboratory. Prior to their arrival, participants were permitted to eat a light meal no less than 2 hours prior and were asked to arrive well hydrated as no fluid replacements were provided during the experiment. They were instructed to drink \(~500\) mL of water before going to bed the night before the experimental session as well as upon waking in the morning. Upon arriving at the laboratory, participants changed into shorts and sandals and provided a urine sample for the assessment of urine specific gravity (model TS400, Reichter Inc., Depew, NY, USA). Euhydration was defined as a urine specific gravity value of \(\leq 1.020\) (31). Participants were instrumented in a non-heat stress environment (\(~23^\circ C\)). They were then transferred into the Snellen whole-body air calorimeter regulated to an ambient temperature of \(40^\circ C\) and \(~15\%\) relative humidity, where they rested for a 30-min
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habituation period in an upright semi-recumbent position. Participants then performed three successive 30-min bouts of cycling at increasingly greater rates of metabolic heat production of 150 (low), 200 (moderate) and 250 (high) W·m⁻². Increases in metabolic rate augments the rate that heat must be dissipated (32). These rates of metabolic heat production were equivalent on average to 36 ± 6%, 49 ± 7%, and 61 ± 9% of the participant’s pre-determined VO₂peak for the low, moderate, and high heat loads, respectively. Each exercise bout was followed by a 15-min recovery period. We employed a fixed rate of metabolic heat production to ensure a similar level of heat stress and therefore thermal drive for heat loss between participants (32).

Measurements

The Snellen whole-body direct air calorimetry was used to measure the rates of whole-body evaporative and dry heat exchange with an accuracy of ± 2.3 W (33). The calorimeter inflow and outflow values of absolute humidity and air temperature were collected at 8-sec intervals. Absolute humidity was measured using high precision dew point hygrometry (RH Systems model 373H, Albuquerque, NM, USA), whereas air temperature was measured using high precision resistance temperature detectors (± 0.002°C, Black Stack model 1560, Hart Electronics, UT, USA). Air mass flow through the calorimeter was measured by differential thermometry over a known heat source placed in the effluent air stream. The real-time data for absolute humidity, air temperature and air mass flow were displayed and recorded on a personal computer with LabVIEW software (Version 7.0, National Instruments, Austin, TX, USA). The rate of evaporative heat loss was calculated using the calorimeter outflow – inflow difference in absolute humidity, multiplied by the air mass flow (kg air·s⁻¹) and the latent heat of vaporization of sweat (2,426 J·g sweat⁻¹). The rate of dry heat loss was calculated using the calorimeter outflow – inflow difference in air temperature, multiplied by the air mass flow and specific
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heat capacity of air (1,005 J·kg air⁻¹·°C⁻¹). Evaporative heat loss was expressed as positive values, whereas a negative value for dry heat loss signified a heat gain from the environment (i.e., ambient temperature exceeded that of the skin throughout the exercise protocol). Rate of oxygen consumption, carbon dioxide production and minute ventilation were derived from continuous measures of expired gases and air flows (Moxus modular metabolic system, AEI Technologies, Bastrop, TX, USA), and used to estimate metabolic heat production (32). To account for respiratory heat exchange, expired air was recycled back into the calorimeter.

Core temperature was measured at the rectum by inserting a paediatric thermocouple probe (Mon-a-therm General Purpose Temperature Probe, Mallinckrodt Medical, St. Louis, MO) 12 cm past the anal sphincter. For some participants (n=3 for Control; n=3 for T2D), core temperature was measured at the esophagus whereby the same thermocouple probe was inserted 40 cm past the entrance of the nostril while the participant drank water through a straw (~250 mL of water). Mean skin temperature was calculated as the weighted average of the temperature measured at four skin sites: biceps 30%, chest 30%, thigh 20%, and calf 20% (34). All temperature data were collected at 15 second intervals and were displayed and recorded in spreadsheet format using a HP Agilent data acquisition module (model 3497A; Agilent Technologies Canada, Mississauga, ON, Canada) and a personal computer with LabVIEW software (version 7.0, National Instruments, Austin, TX, USA).

Local sweat rate was measured using 2.8 cm² ventilated capsule fixed to the thigh, chest, upper back, and mid-anterior forearm with an adhesive ring and topical skin glue (Collodion HV; Mavidon Medical Products, Lake Worth, FL). Anhydrous compressed air was circulated through the capsules at a rate of 1.0 L/min. The vapor density of the effluent air was measured using dew point hygrometry (Model HMT333, Vaisala, Helsinki, Finland). Sweat rate was calculated every 5 seconds using the water content of the effluent air multiplied by flow rate and normalized for the skin surface area under the
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capsule (mg\(^{-1}\)min\(^{-1}\)cm\(^{-2}\)). Heart rate was recorded at 15 sec intervals using a Polar coded transmitter and stored with a PolarRS400 interface and Polar Pro Trainer 5 software (Polar Electro, Oy, Finland). Due to technical difficulties in some trials, local sweat rate was not recorded for some participants on the thigh (Control: n=1; T2D: n=3), chest (Control: n=2; T2D: n=2), upper back (T2D: n=1), and mid-anterior forearm (T2D: n=1), whereas heart rate was not collected for one T2D participant.

Data analysis

Minute averages were calculated for all time-dependent variables, with an average of the last 5-min of baseline rest and each exercise bout used for statistical analyses. The change in body heat storage during each exercise bout was measured as the temporal summation of the net heat load (the combined heat generated by exercise and gained from the environment) and evaporative heat loss (32). The cumulative (total) amount of heat stored was calculated as the sum over the three exercise bouts. Heart rate responses were presented in absolute values as well as expressed as a percentage of heart rate reserve calculated using the following equation:

\[
\% \text{ Heart rate reserve} = \frac{HR_t - HR_{bl}}{HR_{max} - HR_{bl}} \cdot 100
\]

where \(HR_t\) is the heart rate at a given time point (beats min\(^{-1}\)), \(HR_{bl}\) is the baseline heart rate (beats min\(^{-1}\)), and \(HR_{max}\) is the participant’s measured maximal heart rate during the incremental exercise test (beats min\(^{-1}\)).

The physiological strain index was calculated from the measurements of core temperature and heart rate using the following equation (35):

\[
\text{Physiological strain index} = 5 \cdot \frac{T_{cor} - T_{cobl}}{39.5 - T_{cobl}} + 5 \cdot \frac{HR_t - HR_{bl}}{HR_{max} - HR_{bl}}
\]
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where $T_{co,t}$ is the core temperature recorded at a given time point ($^\circ$C), $T_{co,bl}$ is the core temperature recorded at baseline ($^\circ$C), $HR_t$ is the heart rate recorded at a given time point (beats min$^{-1}$), and $HR_{bl}$ is the heart rate recorded at baseline (beats min$^{-1}$).

Statistical analysis

Our primary analysis consisted of evaluating within- and between-group changes in the rates of metabolic heat production, dry heat exchange, net heat load, and evaporative heat loss as well as core and mean skin temperatures, heart rate, percentage of heart rate reserve, physiological strain index, and local sweat rates during the final 5 min of each exercise bout. Data were analyzed using a two-way ANOVA with the non-repeated factor of group (2 levels: T2D and Control) and repeated factor of exercise (3 levels: low, moderate, high). We also used a two-way ANOVA with a repeated factor of exercise time (6 levels: 5, 10, 15 20, 25 and 30 min) and a non-repeated factor of group (2 levels: T2D and Control) to compare whole-body evaporative heat loss between groups within each exercise bout separately to determine at what time point any between-group differences in evaporative heat loss occurred. When a main effect or interaction was detected, post-hoc comparisons were carried out using unpaired $t$ tests. Unpaired $t$ tests were used to compare physical characteristics, baseline values, and cumulative changes in body heat storage over the three exercise bouts, the three recovery periods, and over the three/exercise recovery cycles between groups. The level of significance for all analyses was set at $P \leq 0.05$. All data are reported as means (SD). All statistical analyses were conducted using SPSS 25 (IBM, Armonk, NY, USA) statistical software.
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RESULTS

Physical characteristics and hydration status

There were no between-group differences in age, height, body mass, surface area, fat percentage, body mass index, and \( \dot{VO}_{2\text{peak}} \) (all \( P>0.05 \), Table 1). Pre-trial urine specific gravity was similar between groups (T2D: 1.018 ± 0.006; Control: 1.014 ± 0.007, \( P=0.11 \)), confirming that participants were similarly and adequately hydrated prior to the start of the experimental trial.

Whole-body heat exchange

Baseline metabolic heat production (T2D: 57 ± 7 W m\(^{-2}\); Control: 53 ± 8 W m\(^{-2}\)), dry heat gain (T2D: -39 ± 9 W m\(^{-2}\); Control: -39 ± 8 W m\(^{-2}\)), net heat load (T2D: 96 ± 6 W m\(^{-2}\); Control: 92 ± 12 W m\(^{-2}\)), and evaporative heat loss (T2D: 74 ± 13 W m\(^{-2}\); Control: 83 ± 16 W m\(^{-2}\)) were not different between groups (all \( P>0.05 \)). By design, metabolic heat production increased across exercise bouts (main effect of time: \( P<0.01 \)) but did not differ between groups (main effect of group: \( P=0.75 \)), averaging 155 ± 9 (low), 204 ± 14 (moderate) and 257 ± 15 W m\(^{-2}\) (high) across groups. Dry heat gain was similar across exercise bouts and between groups (both \( P>0.05 \)), averaging -48±14 W m\(^{-2}\) in both groups across the three exercise bouts. Consequently, the net heat load increased across exercise bouts (\( P<0.01 \)) and was comparable between groups (\( P=0.75 \)) for all exercise bouts (Figure 1). Evaporative heat loss also increased across exercise bouts (\( P<0.01 \)) but differed between groups (\( P=0.04 \)), such that it was lower during the moderate (\( P=0.04 \)) and high (\( P=0.03 \)), but not low (\( P=0.12 \)) exercise-induced heat loads for T2D relative to Control (Figure 1). Our secondary analysis revealed a group*time interaction for evaporative heat loss during both the moderate (\( P<0.01 \)) and high (\( P=0.03 \)) exercise conditions, with the evaporative heat loss response being significantly lower for T2D compared to Control from 10 to 30 min during moderate-intensity exercise and from 15 min to 30 min during high-intensity exercise (all
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P<0.05, Figure 1). The net effect of this attenuation was a greater change in body heat storage (group*time interaction: P=0.05) for T2D compared to Control during both the moderate and high heat loads (both P<0.01, Figure 2), with a trend toward significance at the low condition (P=0.06). Consequently, a 27% greater increase in body heat storage was measured over the three exercise bouts for T2D relative to the Control group (P=0.01, Figure 2).

Core and mean skin temperatures, heart rate, and physiological strain index

Core (T2D: 37.1 ± 0.2°C; Control: 37.1 ± 0.3°C) and mean skin (T2D: 35.5 ± 0.5°C; Control: 35.3 ± 0.4°C) temperatures were not different between groups during the baseline resting period (both P>0.05). Core temperature increased across exercise bouts (P<0.01), albeit there was no significant difference between groups (P=0.15). Similarly, the relative change in core temperature from baseline resting increased with each exercise bout (P<0.01), however a greater increase was measured in T2D compared to Control (P=0.01) at the end of all three exercise-induced heat loads (all P<0.05, Figure 3). Mean skin temperature increased across exercise bouts (p<0.01), with a trend observed between groups (P=0.08) at the low (T2D: 35.8 ± 0.4°C; Control: 35.6 ± 0.4°C), moderate (T2D: 36.0 ± 0.5°C; Control: 35.7 ± 0.5°C), and high (T2D: 36.3 ± 0.6°C; Control: 36.0 ± 0.5°C) exercise-induced heat loads.

Baseline heart rate was greater for T2D compared to Control (P=0.01, Figure 3). Thereafter, heart rate increased across exercise bouts (P<0.01), with a greater response measured for the T2D relative to the Control group at the end of each exercise bout (P=0.02, Figure 3). To account for between-group differences in baseline resting and maximal heart rate, heart rates were expressed as a percentage of heart rate reserve. There was a group by time interaction (P=0.03) for heart rate reserve such that the level achieved at the end of the high condition was greater for T2D (82 ± 15%) compared to Control (69 ± 18%, P=0.04), but similar between groups during the low (T2D: 32 ± 12%; Control: 29
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± 8%, P=0.41) and moderate (T2D: 55 ± 13%; Control: 47 ± 14%, P=0.09) exercise conditions, respectively. Because of the differences in core temperature and heart rate, the physiological strain index also increased across exercise bouts (P<0.01), with the increase being greater in T2D compared to Control (P=0.02) at the end of all three exercise conditions (all P<0.05, Figure 3).

Local sweat rates

Baseline local sweat rates on the thigh, chest, upper back, and mid-anterior forearm did not differ between groups (Table 2). Thereafter, sweat rates at all sites increased across exercise bouts (all P<0.01), with no significant differences measured between groups throughout exercise (all P>0.05, Table 2).

DISCUSSION

In the present study, time-dependent changes in whole-body dry and evaporative heat exchange were assessed in habitually active older males with and without T2D during exercise at increasing fixed rates of metabolic heat production in hot, dry conditions. Using this experimental design, we showed that habitually active older males with well-controlled T2D exhibit similar whole-body dry heat exchange, but reduced whole-body evaporative heat loss during exercise compared to their healthy non-diabetic counterparts with matched physical characteristics and aerobic fitness. However, this impairment only occurred at exercise-induced heat loads ≥200 W.m⁻², with the magnitude of that impairment becoming greater with increases in heat load and therefore level of heat stress. As a consequence of their reduced capacity to dissipate heat, the individuals with T2D stored increasingly more heat over each exercise bout, leading to a 27% greater change in heat storage over the three exercise bouts. This greater change in whole-body heat storage was paralleled by greater increases in
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core temperature, heart rate, and physiological strain index throughout the exercise protocol, as well as a greater change in percentage heart rate reserve by the end of the highest heat load employed.

Reductions in whole-body evaporative heat loss have been demonstrated previously in sedentary older adults with T2D during exercise at a single heat load (22). However, it remained unknown whether T2D-mediated impairments in evaporative heat loss also exist in habitually active older adults with T2D or whether those impairments, if present, would worsen with increases in the exercise-induced heat load. With our unique approach, we were able to show for the first time, that even habitually active older males with well-controlled T2D display a slower rise in whole-body evaporative heat loss and a reduced end-exercise response compared to their nondiabetic counterparts during moderate-intensity exercise (200 W/m²), with the magnitude of this this impairment becoming worse at the high exercise-induced heat load (Figure 1). Consequently, the T2D group stored progressively more heat with each successive exercise bouts, as evidenced by an interaction between group and exercise intensity (Figure 2). Due to the short exercise duration employed (i.e., 30 min), evaporative heat loss did not achieve a plateau in both groups as this has been shown to take up to 45 min to occur (32). However, in our previous study (22), the T2D-mediated impairments in evaporative heat loss persisted for the full duration of a 60 min continuous exercise bout, albeit the difference between groups became less pronounced over time. Therefore, it is likely that the mean reduction of ~10% in evaporative heat loss and the ensuing ~41% greater mean increase in body heat storage for T2D during moderate and high-intensity exercise would be sustained during exercise of longer duration, which would exacerbate the difference in body heat storage between groups for a given heat load. Theoretically, these differences would translate into a greater change in mean body temperature of ~0.6°C•per hour (assuming a body mass of 70 kg with a specific heat capacity of 3.47 kJ•kg⁻¹•°C⁻¹) for T2D relative to Control during moderate- to high-
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intensity exercise. Ultimately, this could increase the chance of heat-related illness during prolonged exercise and/or with increases in environmental heat load (i.e., higher ambient temperatures).

In contrast to the marked reduction in evaporative heat loss, T2D did not affect whole-body dry heat exchange. This implies that T2D-mediated reductions in local skin blood flow reported in previous studies (13, 15-17, 36, 37) may not contribute to the impairments in whole-body heat dissipation during exercise. However, we cannot discount the possibility that reductions in skin blood flow may have reduced blood-borne heat delivery to the skin surface, and thus, contributed to the observed reductions in evaporative cooling observed in the T2D group, especially given that mean skin temperature was similar between groups throughout the intermittent exercise protocol. While our study provides novel insight into the influence of T2D on dry and evaporative heat exchange in habitually active older males as a function of increasing heat loads (and therefore levels of heat stress), future work is necessary to examine whether our observations would persist at the same heat load, but in a cooler environment that permits a thermal gradient for dry heat loss.

The impairments in whole-body evaporative heat loss and greater heat storage in the individuals with T2D were paralleled by a more pronounced increase in core temperature (Figure 3). During exercise, the demand for skin blood flow increases as core temperature becomes greater (38). As a result of the increased demand for skin blood flow, which is necessary to promote heat transfer to the skin surface, heart rate rises to maintain and/or increase cardiac output to meet the metabolic demands (i.e., muscle blood flow) of the exercise as well as to preserve blood pressure (38). This increase in heart rate can also be directly stimulated by core temperature itself as well as indirectly due to the effect of hyperthermia on sympathetic outflow (39). Therefore, it is not surprising that the greater thermal strain (i.e. greater increase in body heat storage and core temperature) experienced by the T2D group was paralleled by a more pronounced increase in heart rate throughout the exercise protocol (Figure 3).
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However, it is important to note that the individuals with T2D possessed a greater baseline heart rate relative to their healthy counterparts, an observation that has been, in part, ascribed to autonomic nervous system dysfunction (40), which can often pre-date or occur early after T2D diagnosis (41, 42). When this disparity was considered, cardiovascular strain was still greater for T2D as evidenced by a 15% greater rise in heart rate reserve by the end of the high heat load condition relative to Control. These differences in core temperature and heart rate led to ~25% greater physiological strain index throughout the exercise protocol in the T2D relative to their non-diabetic counterparts (Figure 3). Altogether, our findings demonstrate that even older males with T2D, who perform regular physical activity and possess a higher level of aerobic fitness, may be at greater risk of heat-related injury (e.g., heat exhaustion, heat syncope, heat stroke), work-related injuries (i.e., due to increases in hyperthermia-induced fatigue), and/or adverse cardiovascular events, compared to healthy habitually active older males, especially during more strenuous work or physical activity in hot environments (i.e., higher heat loads).

While we observed a reduction in whole-body evaporative heat loss in the individuals with T2D at the moderate and high exercise-induced heat loads (Figure 1), this was not paralleled by similar differences in local sweat rate at any of the regions measured (thigh, chest, forearm, upper back) (Table 2). This was surprising, as individuals with T2D have been shown to display differences in upper and lower body sweating and sometimes complete anhydrosis of the lower body (19-21). These outcomes therefore highlight the limitations associated with measuring sweat rate from only small areas of the body surface (~2.8 cm²), which may not be representative of T2D-mediated impairments in the evaporation of sweat secreted by the ≥2 million sweat glands dispersed across the body. The use of whole-body direct calorimetry in this study allowed us to quantify the integrated effect of all those sweat glands and provided an accurate time-dependent assessment of whole-body evaporative heat loss (and
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therefore sweat production) in habitually active older males with T2D. Given the difficulties associated with the latter and given the small number of skin sites measured in this study, additional research is required to determine if certain skin sites (or combination of sites), including others than the ones measured in this study (e.g., forehead, lower back, abdomen, calf, hands and feet, etc.), might better reflect changes in whole-body sweat production, and therefore evaporative capacity in the T2D population.

**Considerations**

We excluded individuals who had clinically diagnosed T2D-related complications (i.e., peripheral and/or autonomic neuropathy, and others) or very poor glycemic control (HbA1c >9.9%); factors known to be associated with greater impairments in skin blood flow and sweating on the extremities (i.e., hands and feet) among individuals with T2D (8). Therefore, it currently remains unclear if these greater impairments in local heat loss responses would translate into further reductions in whole-body heat dissipation during exercise in the heat and if these differences might compromise the body’s capacity to dissipate heat to a greater extent such that differences occur at even lower levels of heat stress or whether other regions of the body might compensate to preserve the body’s capacity to dissipate heat. Furthermore, it also remains unknown how T2D modulates whole-body evaporative heat loss in more humid environments common to many places around the world (e.g., Europe, North America, South America, Asia, and Africa) and various physically demanding occupations (e.g., mining, electric utilities, others). In such conditions, individuals of all ages store significantly more heat and experience greater levels of hyperthermia (43, 44). However, recent studies have shown that age-related impairments in whole-body evaporative heat loss persisted during exercise in more humid conditions (43, 44). Therefore, it is possible that the T2D-mediated impairments in whole-body evaporative heat
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loss observed in this study may also be sustained under such environments placing this population at an even greater risk of heat-related illness. Nonetheless, this represents an important area of future research.

**Perspectives and significance**

Currently, Diabetes Canada and the American Diabetes Association recommends that individuals with T2D should avoid performing strenuous physical activity in the heat (23, 45). This is because heat stress is associated with an increase in disease-related symptoms as well as a greater level of dehydration due to hyperglycemia and/or medication use, which can exacerbate the risk of heat-related morbidity and mortality in this population group (8). While sedentary older adults with T2D are especially at risk (8, 22), our findings demonstrate that the risk is omnipresent in habitually active older adults who perform regular physical activity to manage their disease (i.e., improve glycemic control, lipid profile, cardiovascular health and control weight) (23, 45). These impairments in heat dissipation were evident during moderate-to-high intensity exercise, despite the fact that maintaining a higher aerobic fitness helps has been shown to delay age-related reduction in heat loss capacity in older men (4). Therefore caution is warranted when older adults with T2D perform physical work that require extended periods of walking/running and/or rapid movements (pushing and pulling) in an occupational setting (i.e., electrical utilities, firefighting, mining, farming, and others) as well as during recreational activities (i.e., walking, jogging, cycling, aerobics and calisthenics, and various other sporting activities) (46). Nevertheless, further research is necessary to delineate strategies and interventions that can enhance whole-body heat loss in this population group. In this regard, several studies have shown that performing repeated bouts of exercise in the heat (i.e., heat acclimation) can markedly improve the body’s capacity to dissipate heat (47). No study to date, however, has assessed the extent to which T2D-mediated impairments in heat loss capacity may be reduced by heat. Furthermore, passive heat therapy (i.e., sauna bathing, limb and/or
whole-body hot water immersion) has recently garnered considerable interest due to its effectiveness in improving vascular and autonomic function in young and older adults (48-50), enhancing cardiac function and exercise capacity in adults with congestive heart failure (51), as well as improving glycemic control in adults with T2D (52). Conversely, it remains unknown how this intervention method alone or in combination with exercise training may help improve whole-body heat dissipation, and possibly reduce thermal and cardiovascular strain experienced by older adults with T2D during exercise in the heat.

CONCLUSIONS

We showed for the first time that T2D impairs whole-body evaporative heat loss in a heat load-dependent manner such that impairments in habitually active older males with well-controlled T2D are first evident at moderate levels of heat stress (i.e., exercise-induced heat load of ≥200 W m⁻²) with the magnitude of those differences becoming greater with increasing exercise intensity when performed in a hot, dry environment. Consequently, the T2D group experienced higher levels of thermal and cardiovascular strain as evidenced by greater increases in whole-body body heat storage, core temperature, heart rate, percentage of heart rate reserve, and physiological strain compared to their age-matched non-diabetic counterparts.

ACKNOWLEDGMENTS

The authors are indebted to the study participants for the success of this study. The authors would also like to thank Ms. Sheila Dervis and all other members of the Human and Environmental Physiology Research Unit who assisted with data collection.
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GRANTS

The study was conducted at the Human and Environmental Physiology Research Unit (HEPRU). This study was funded by the Canadian Institutes of Health Research (Grant number 286363, held by G. P. Kenny). G. P. Kenny was supported by a University of Ottawa Research Chair Award. M. P. Poirier was supported by Natural Sciences and Engineering Research Council of Canada Alexander Graham Bell Scholarship (CGS-D), HEPRU, as well as the University of Ottawa. S.R. Notley was supported by a Postdoctoral Fellowship from HEPRU. R. J. Sigal was supported by a Health Senior Scholar award from Alberta Innovates-Health Solutions.

AUTHOR CONTRIBUTIONS

M.P.P., P.B., J.M., R.J.S., A.D.F., and G.P.K. conceptualized and designed the research. M.P.P. performed experiments. M.P.P. performed data analysis. All authors interpreted the experimental results. M.P.P. prepared figures and drafted manuscript. All authors edited and revised the manuscript. All authors approved the final version of the manuscript.
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Table 1. Participant characteristics

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<th>Age (years)</th>
<th>Height (cm)</th>
<th>Mass (kg)</th>
<th>BSA (m²)</th>
<th>Body fat (%)</th>
<th>BMI (kg m⁻²)</th>
<th>VO₂peak (mL·kg⁻¹·min⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T2D (n=16)</td>
<td>58 ±6</td>
<td>174 ± 5</td>
<td>84.2 ± 11.6</td>
<td>1.99 ± 0.13</td>
<td>26.8 ± 5.4</td>
<td>27.7 ± 3.6</td>
<td>33.3 ± 7.0</td>
</tr>
<tr>
<td>Control (n=16)</td>
<td>60 ± 4</td>
<td>176 ± 5</td>
<td>82.7 ± 11.7</td>
<td>1.99 ± 0.14</td>
<td>24.6 ± 8.8</td>
<td>26.7 ± 3.6</td>
<td>37.2 ± 5.7</td>
</tr>
</tbody>
</table>

Notes. Values are mean ± SD. T2D, type 2 diabetes. BSA, body surface area. BMI, body mass index. VO₂peak, peak aerobic power.
Type 2 diabetes and exercise heat stress

Table 2. Local sweat rate on the thigh, chest, upper back and mid-anterior forearm in older habitually active males with (T2D, n=16) and without (Control, n=16) T2D at baseline and during three 30-min bouts of cycling at increasing fixed rates of metabolic heat production of 150 (low), 200 (moderate), and 250 (high) W m\(^{-2}\), each followed by a 15-min recovery period in a hot, dry environment (40°C, ~15% relative humidity).

<table>
<thead>
<tr>
<th></th>
<th>Group</th>
<th>Baseline</th>
<th>Low</th>
<th>Moderate</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>LSR Thigh</td>
<td>T2D</td>
<td>0.29 ± 0.16</td>
<td>0.55 ± 0.24</td>
<td>0.64 ± 0.26</td>
<td>0.70 ± 0.29</td>
</tr>
<tr>
<td>mg(^{-1})min(^{-1})cm(^{-2})</td>
<td>Control</td>
<td>0.50 ± 0.35</td>
<td>0.78 ± 0.53</td>
<td>0.90 ± 0.59</td>
<td>0.97 ± 0.61</td>
</tr>
<tr>
<td>LSR chest</td>
<td>T2D</td>
<td>0.53 ± 0.30</td>
<td>0.89 ± 0.42</td>
<td>1.06 ± 0.45</td>
<td>1.19 ± 0.46</td>
</tr>
<tr>
<td>mg(^{-1})min(^{-1})cm(^{-2})</td>
<td>Control</td>
<td>0.43 ± 0.23</td>
<td>0.88 ± 0.43</td>
<td>1.15 ± 0.52</td>
<td>1.37 ± 0.54</td>
</tr>
<tr>
<td>LSR upper back</td>
<td>T2D</td>
<td>0.47 ± 0.25</td>
<td>0.85 ± 0.47</td>
<td>1.03 ± 0.55</td>
<td>1.13 ± 0.61</td>
</tr>
<tr>
<td>mg(^{-1})min(^{-1})cm(^{-2})</td>
<td>Control</td>
<td>0.46 ± 0.26</td>
<td>0.91 ± 0.40</td>
<td>1.20 ± 0.51</td>
<td>1.42 ± 0.59</td>
</tr>
<tr>
<td>LSR mid-anterior forearm</td>
<td>T2D</td>
<td>0.34 ± 0.13</td>
<td>0.68 ± 0.26</td>
<td>0.88 ± 0.33</td>
<td>0.96 ± 0.40</td>
</tr>
<tr>
<td>mg(^{-1})min(^{-1})cm(^{-2})</td>
<td>Control</td>
<td>0.39 ± 0.18</td>
<td>0.76 ± 0.30</td>
<td>0.97 ± 0.43</td>
<td>1.10 ± 0.47</td>
</tr>
</tbody>
</table>

**Notes.** Values are expressed as mean ± SD. LSR, local sweat rate. Due to technical difficulties in some trials, local sweat rate was not collected for some participants on the thigh (T2D: 3; Control: 1), chest (T2D: 2; Control: 2); upper back (T2D: 1), and mid-anterior forearm (T2D: 1). There were no significant differences between groups, all P>0.05.
Figure 1. Whole-body net heat load (metabolic heat production ± dry heat gain, dotted line) and evaporative heat loss in older habitually active males with (T2D, n=16) and without (Control, n=16) T2D at baseline and during three 30-min bouts of cycling at increasing fixed rates of metabolic heat production of 150 (low), 200 (moderate), and 250 (high) W m$^{-2}$, each followed by a 15-min recovery period (Rec1, Rec2, Rec3) in a hot, dry environment (40°C, ~15% relative humidity). The net heat load is presented as the mean across groups, whereas evaporative heat loss is expressed as the mean ± SD within each group. (*) Significant difference between groups, P≤0.05.
Figure 2. Change in whole-body heat storage (mean ± SD) for older habitually active males with (T2D, n=16) and without (Control, n=16) T2D during three 30-min bouts of cycling at increasing fixed rates of metabolic heat production of 150 (low), 200 (moderate), and 250 (high) W m⁻² in a hot, dry environment (40°C, ~15% RH). The total (sum) change in body heat storage measured over the three exercise bouts is also presented. (†) Group*time interaction across the three exercise bouts, P<0.05. (*) Significant difference between groups, P≤0.05.
Figure 3. The change (mean ± SD) in absolute (A) and relative (B) core temperature as well as heart rate (C) and physiological heat strain index (D) in older habitually active males with (T2D) and without (Control) T2D at baseline and during three 30-min bouts of cycling at increasing fixed rates of metabolic heat production of 150 (low), 200 (moderate), and 250 (high) W m⁻², each followed by a 15-min recovery period (Rec1, Rec2, Rec3) in a hot, dry environment (40°C, ~15% relative humidity). Heart rate was not collected for one T2D participant due to technical difficulties. (*) Significant difference between groups, P≤0.05.
Type 2 diabetes and short-term heat acclimation

3.3. Thesis article #3

Differential effects of short-term heat acclimation on whole-body heat exchange in habitually active older males with and without type 2 diabetes

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Word count: 8,265 words

Running head: Type 2 diabetes and short-term heat acclimation

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Type 2 diabetes and short-term heat acclimation

ABSTRACT

Heat acclimation mediated by acute exercise training can attenuate age-related impairments in heat loss. It remains unclear however, if a similar benefit can be conferred to older adults with type 2 diabetes (T2D) who experience greater age-related impairments in heat dissipation relative to their healthy counterparts. We used direct calorimetry to assess whole-body evaporative heat loss prior to (day 0) and following (day 8) seven days of heat acclimation (90 min cycling at 50% \( \dot{V}O_{2\text{peak}} \)) in eighteen older (mean±SD; 60±6 years) habitually active (peak aerobic power [\( \dot{V}O_{2\text{peak}} \): 35.2±6.5 mL·kg\(^{-1}\)·min\(^{-1}\)]) males with (n=8, HbA1c: 6.9±1.0%) and without (Control, n=10) T2D matched for age and \( \dot{V}O_{2\text{peak}} \). On days 0 and 8, participants performed three 30-min bouts of cycling at increasing fixed rates of metabolic heat production (and therefore heat load) of 150 (low), 200 (moderate), 250 (high) \( \text{W} \cdot \text{m}^{-2} \) (equal to ~37, ~49, and ~61 of \( \dot{V}O_{2\text{peak}} \), respectively), each followed by 15-min recovery, in dry-heat (40°C, ~15% relative humidity). Impairments in evaporative heat loss were observed during the moderate (T2D: 216±25; Control: 237±16 \( \text{W} \cdot \text{m}^{-2} \), \( P=0.04 \)) and high (T2D: 242±29; Control: 276±26 \( \text{W} \cdot \text{m}^{-2} \), \( P=0.02 \)) heat loads for T2D relative to Control on day 0. Consequently, heat acclimation increased evaporative heat loss by as much as 13±5% in T2D group, whereas it was only increased by as much as 6±6% in the Control group (\( P=0.01 \)). Therefore, no differences were evident at the moderate (T2D: 239±25; Control: 254±16 \( \text{W} \cdot \text{m}^{-2} \), \( P=0.15 \)) and high (T2D: 279±27; Control: 294±19 \( \text{W} \cdot \text{m}^{-2} \), \( P=0.21 \)) heat loads on day 8. As a result, body heat storage (summation of heat production/loss) was also similar between groups following heat acclimation (T2D: 380±172 \( \text{kJ} \); Control: 297±116 \( \text{kJ} \), \( P=0.14 \)). We show that short-term heat acclimation abolishes T2D-related impairments in whole-body evaporative heat loss during exercise in hot, dry conditions.

Keywords: Aging, hyperthermia, diabetes, exercise, heat acclimatization, heat stress, sweating.
Type 2 diabetes and short-term heat acclimation

INTRODUCTION

Heat-related morbidity and mortality is increased in older adults during extreme heat events (1, 2) and exercise-induced heat stress (3), especially in those with type 2 diabetes (T2D) (4-6), relative to the general population. This has been ascribed, in part, to T2D-related reductions in regional (i.e., torso, limbs, and extremities) sweat production (7-9), which lead to attenuated whole-body evaporative heat loss (and therefore whole-body sweat production) in habitually active older males with T2D compared to healthy habitually active older males during exercise in the heat (10, 11). This reduction in sweat evaporation, which is our primary avenue of heat loss in hot conditions, exacerbates body heat storage relative to healthy older males during exercise in the heat (10, 11), particularly at moderate-to-high exercise intensities (50 to 60% of peak aerobic power (\(\dot{V}O_{2\text{peak}}\)) (11). The well-documented T2D-mediated impairments in cardiovascular function (i.e., reduced vascular and autonomic function, cardiac output, and blood pressure regulation) (12-21) are likely exacerbated by the greater heat strain associated to the reduction in heat dissipation during physical activity/work in the heat.

It is well established that performing moderate-intensity aerobic exercise (~50-60% of \(\dot{V}O_{2\text{peak}}\)) for 60-90 min·day\(^{-1}\) in the heat for five or more consecutive days (i.e., heat acclimation) can induce functional adaptations to the sweating response in both young and older adults (22-26). Those adaptations occur gradually as a function of the rise in body temperature (adaptation stimulus) each day (26), with the magnitude of adaptation to a given adaptation stimulus being dependent upon one’s accommodation “reserve”, which is defined by the pre-adaptation baseline and the genetically pre-determined physiological maximum (26). This concept is analogous to endurance-training, whereby the improvements in aerobic power will be markedly greater in sedentary individuals as compared to healthier, more physically active individuals, for the same training stimulus (27). Since sedentary and habitually active older adults with T2D have a lower physiological capacity to dissipate heat compared
Type 2 diabetes and short-term heat acclimation to older adults without T2D prior to heat acclimation (i.e., pre-adaptation baseline) (10, 11), it is possible that older adults with T2D may possess a greater accommodation reserve (i.e., capacity to adapt). As such, older adults with T2D may display an enhanced magnitude of adaptation to the sweating response to a given adaptation stimulus relative to sedentary and habitually active healthy older adults. While this notion is theoretically possible, the reverse is also conceivable, such that adults with T2D may have a compromised ability to physiologically adapt to a given adaptation stimulus compared to adults without T2D due to their overall reduction in physiological function (i.e., altered sweat glands and skin vasculature, impaired autonomic and/or cardiovascular function, etc.) (28). Nevertheless, while a growing body of research shows that exercise training (i.e., walking, jogging, or cycling) can improve glycemic control and cardiovascular function, as well as reduce body mass, waist circumference and body adiposity in adults with T2D (28-33), no study to our knowledge has been designed to assess the effects of exercise training, either in temperate and/or hot conditions, on thermoregulatory function in adults with T2D.

The purpose of this study was to assess time-dependent changes in whole-evaporative heat loss in habitually active (i.e., ≥3–4 days per week of continuous exercise of 30–60 min per session) older males with and without well-controlled T2D (i.e., HbA1c ≤9.9 % and no complications) during exercise at increasing, fixed rates of metabolic heat production of 150 (low), 200 (moderate), and 250 W m⁻² (high) in hot, dry conditions, performed prior to and following a 7-day traditional heat acclimation protocol (90 min of daily cycling at 50% \( \bar{V}O_2\text{peak} \)). This incremental exercise model was used since improvements in evaporative heat loss during heat acclimation become more evident at higher exercise-induced heat load (25), as do T2D-mediated impairments in evaporative heat loss (11). We hypothesized that heat acclimation would enhance whole-body evaporative heat loss in both groups, albeit the magnitude of adaptation would be greater with increasing levels of heat stress, possibly to a greater
Type 2 diabetes and short-term heat acclimation extent for those with T2D. This information is critical since performing regular physical activity has long been recommended to optimize glycemic control and prevent disease-related complications (i.e., neuropathy) in adults with T2D, although it is recognized that they may be at an increased risk of heat-related injury and/or death when exercise is performed in the heat due to their impaired capacity to dissipate heat (30). However, it is possible that older adults with T2D respond more like their healthy counterparts following short-term heat acclimation which would reduce their risk of heat-related illness during exercise in the heat.

MATERIALS AND METHODS

Ethical approval

The experimental protocol was approved by the University of Ottawa Health Sciences and Science Research Ethics Board in accordance with the Declaration of Helsinki. All volunteers provided written, informed consent before participating in the study.

Participants

Eighteen habitually active, but not endurance trained, older males with (T2D, n=8) and without T2D (Control, n=10) participated in this study (Table 1). Five T2D and three Control participants from the second study took part in this study. Participants were selected based on their age and VO₂peak to minimize between-group differences in age and aerobic fitness, so that the independent effects of T2D on the magnitude of adaptation could be examined. All participants with T2D had been diagnosed for ≥5 years and were considered generally healthy, had an HbA1c between 5.5% and 9.0% (mean of 6.9 ± 1.0%), and no clinically diagnosed T2D-related complications (i.e., peripheral and/or autonomic neuropathy, nephropathy, proliferative retinopathy, and unstable cardiac or pulmonary disease). A 3-
Type 2 diabetes and short-term heat acclimation

month recall physical activity questionnaire (34) showed that all participants were habitually active (i.e., ≥3–4 days per week of continuous exercise of 30–60 min per session) and met the physical activity levels recommended by Diabetes Canada (30). All experimental trials were carried out between late October and early May to minimize seasonal acclimatization effects. The respective minimum and maximum daily air temperature averaged -16.4 ± 9.5°C and 14.3 ± 6.9°C during the seven-month acclimation period, with a daily average of -0.8 ± 6.8°C.

**Experimental Protocol**

Participants completed seven consecutive days of heat acclimation (26), during which they cycled daily in dry heat (40ºC, 20% relative humidity) for 90 min at 50% of their pre-determined \( \dot{V}O_2 \text{peak} \). Whole-body heat exchange during exercise was evaluated by direct calorimetry prior to (day 0) and following (day 8) the heat acclimation treatment. Prior to the first calorimetry session, participants completed one screening session where body height was measured using a stadiometer (Detecto, model 2391, Webb City, MO, USA) and body mass was measured using a digital high-performance weighing terminal (model CBU150X, Mettler Toledo Inc., Mississauga, ON, Canada). From these measures, body surface area was calculated (35). Body density was measured using the hydrostatic weighing technique and used to estimate body fat percentage (36). All participants performed an incremental maximal exercise test (37) on a semi-recumbent cycle ergometer (Corival, Lode B. V., Groningen, Netherlands) to determine \( \dot{V}O_2 \text{peak} \) (MCD Medgraphics Ultima Series, MGC Diagnostics, MN, USA). For all healthy males above 55 years of age as well as all participants with T2D, a 12-lead electrocardiogram was performed during the exercise test to detect any cardiac abnormalities. No participants were excluded from the study but one T2D and two Controls withdrew from the study after starting the heat acclimation period.
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**Direct calorimetry sessions (day 0 and day 8).** For the direct calorimetry sessions, participants changed into shorts and sandals as well as provided a urine sample for the assessment of urine specific gravity (model TS400, Reichter Inc., Depew, NY, USA). Euhydration was defined as a urine specific gravity value of <1.020 (38). Participants were instrumented in a non-heat stress environment (~23°C). They were then transferred and seated within the Snellen whole-body air calorimeter regulated to an ambient temperature of 40°C and ~15% relative humidity where they rested for a 30-min habituation period in an upright semi-recumbent position. Participants then performed three successive 30-min bouts of cycling at increasingly greater rates of metabolic heat production of 150 (low), 200 (moderate) and 250 (high) W·m⁻². These rates of metabolic heat production were equivalent to 37 ± 6%, 49 ± 8%, and 61 ± 9% of the participant’s pre-determined \( \tilde{V}O_{2\text{peak}} \) for the low, moderate, and high heat loads, respectively prior to and following heat acclimation. Each exercise bout was followed by a 15-min recovery period. We employed a fixed rate of metabolic heat production to ensure a similar requirement for heat loss between participants and before/after the week of heat acclimation (39).

**Heat acclimation sessions (days 1-7).** On days 1 to 7 inclusively, each participant performed 90 min of exercise on a recumbent cycle ergometer in a thermal chamber regulated at 40°C and 20% relative humidity. Participants were required to exercise at ~50% of their pre-determined \( \tilde{V}O_{2\text{peak}} \). This workload was determined prior to the first heat acclimation session using indirect calorimetry. Participants wore running shorts and shoes for all acclimation sessions. Studies have shown that near complete heat acclimation can take up to 14 days to occur (26). However, we chose this 7-day heat acclimation treatment as it has previously been shown to induce ~75-80% of the total improvements in whole-body evaporative heat loss, body heat storage, rectal temperature and heart rate measured after 14-days in young adult males (25). Therefore, it was selected for this study given that it would be adequate to observe the most important physiological adaptations. Furthermore, this heat acclimation
Type 2 diabetes and short-term heat acclimation regimen was chosen as it provided an equal acclimation stimulus to both groups given they had similar aerobic fitness levels (26).

For all sessions, participants were asked to refrain from consuming alcohol, caffeine, and over-the-counter medications for 24 hours before arriving at the laboratory. Prior to their arrival, participants were permitted to eat a light meal no less than 2 hours prior and were asked to arrive well hydrated as no fluid replacements were provided during the experiment. They were instructed to drink ~500 mL of water before going to bed the night before each session as well as upon waking up in the morning.

**Measurements**

Whole-body direct calorimetry was used to directly measure the rates of whole-body evaporative and dry heat exchange with an accuracy of ± 2.3 W (40). The calorimeter inflow and outflow values of absolute humidity and air temperature were collected at 8-sec intervals. Absolute humidity was measured using high precision dew point hygrometry (RH Systems model 373H, Albuquerque, NM, USA), while air temperature was measured using high precision resistance temperature detectors (± 0.002ºC, Black Stack model 1560, Hart Electronics, UT, USA). Air mass flow through the calorimeter was measured by differential thermometry over a known heat source placed in the effluent air stream. The real-time data for absolute humidity, air temperature and air mass flow were displayed and recorded on a personal computer with LabVIEW software (Version 7.0, National Instruments, Austin, TX, USA). The rate of evaporative heat loss was calculated using the calorimeter outflow – inflow difference in absolute humidity, multiplied by the air mass flow (kg air∙s⁻¹) and the latent heat of vaporization of sweat (2,426 J∙g sweat⁻¹). The rate of dry heat loss was calculated using the calorimeter outflow – inflow difference in air temperature, multiplied by the air mass flow and specific heat capacity of air (1,005 J∙kg air⁻¹∙ºC⁻¹). Evaporative heat loss was expressed as positive values, whereas a negative value for dry heat
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loss signified a heat gain from the environment (i.e., ambient temperature exceeded that of the skin throughout the exercise protocol). Rate of oxygen consumption, carbon dioxide production, and minute ventilation were derived from continuous measures of expired gases and air flows (Moxus modular metabolic system, AEI Technologies, Bastrop, TX, USA), and used to estimate metabolic heat production (39). To account for respiratory heat exchange, expired air was recycled back into the calorimeter.

For all sessions, rectal temperature was measured by inserting a paediatric thermocouple probe (Mon-a-therm General Purpose Temperature Probe, Mallinckrodt Medical, St. Louis, MO) 12 cm past the anal sphincter. For the calorimetry sessions only, mean skin temperature was calculated as the weighted average of the temperature measured at four skin sites: biceps 30%, chest 30%, thigh 20%, and calf 20% (41). All temperature data were recorded at 15 second intervals and were displayed and recorded in spreadsheet format using a HP Agilent data acquisition module (model 3497A; Agilent Technologies Canada, Mississauga, ON, Canada) and a personal computer with LabVIEW software (version 7.0, National Instruments, Austin, TX, USA) during all calorimetry sessions. For all sessions, heart rate was recorded at 15 sec intervals using a Polar coded transmitter and stored with a PolarRS400 interface and Polar Pro Trainer 5 software (Polar Electro, Oy, Finland).

Data analysis

Minute averages were calculated for all time-dependent variables, with an average of the last 5-min of baseline rest and each exercise bout used for statistical analyses of calorimetric (metabolic heat production, evaporative heat loss, dry heat exchange) and thermometric (rectal and mean skin temperatures) as well as heart rate responses (change in percentage of heart rate reserve). Calorimetric variables were expressed relative to body surface area. The rate of increase in whole-body evaporative
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heat loss during exercise was also analyzed by calculating the time constant of the response using an exponential one-phase association nonlinear regression analysis (Prism 7.03, GraphPad, La Jolla, CA). The time constant corresponds to the time taken for evaporative heat loss to reach 63.2% (τ) of the total amplitude achieved during exercise. The magnitude of change in evaporative heat loss was measured as [((post - pre) / post) * 100)]. This analysis was conducted in order to better examine the effect of heat acclimation on heat dissipation (rate of increase and amplitude of change) during the early stages of exercise (25). The change in body heat storage during each exercise bout was measured as the temporal summation of the net heat load (metabolic heat production ± dry heat exchange) and evaporative heat loss (39). The cumulative (total) amount of heat stored was calculated as the sum over the three exercise bouts. To account for between-group differences in the maximal heart rate obtained during the incremental exercise test as well as in baseline heart rate, heart rate data were expressed as a percentage of heart rate reserve calculated using the following equation:

\[
\text{% Heart rate reserve} = \frac{\text{HR}_t - \text{HR}_{bl}}{\text{HR}_{max} - \text{HR}_{bl}} \cdot 100
\]

where \(\text{HR}_t\) is the heart rate at a given time point, \(\text{HR}_{bl}\) is the baseline heart rate and \(\text{HR}_{max}\) is the participant’s measured maximal heart rate during the incremental exercise test.

The physiological strain index was calculated from the measurements of core temperature and heart rate using the following equation (42):

\[
\text{Physiological strain index} = 5 \cdot \frac{T_{ret} - T_{reb}}{39.5 - T_{reb}} + 5 \cdot \frac{\text{HR}_t - \text{HR}_{bl}}{\text{HR}_{max} - \text{HR}_{bl}}
\]

where the rectal temperature \(T_{ret}\) is recorded at a given time point (°C), \(T_{reb}\) is the rectal temperature recorded at baseline (°C), \(\text{HR}_t\) is the heart rate recorded at a given time point (beats min\(^{-1}\)), and \(\text{HR}_{bl}\) is the heart rate recorded at baseline (beats min\(^{-1}\)).
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Statistical analysis

Data collected or derived during the calorimetry sessions were compared using a three-way ANOVA with the non-repeated factor of group (2 levels: T2D and Control) and repeated factor treatment (2 levels: Pre and Post) and exercise bout (3 levels: low, moderate, and high). When a significant interaction or main effect was observed, post hoc comparisons for between-group or between-treatment differences were examined using independent and paired samples t tests, respectively. The physical characteristics of the two experimental groups were also compared using independent-sample t tests. The level of significance for all analyses was set at P≤0.05. All data are reported as means (SD). All statistical analyses were conducted using SPSS 25 (IBM, Armonk, NY, USA) statistical software.

RESULTS

Physical characteristics and hydration status

There were no significant between-group differences in age, height, body mass, body surface area, fat percentage, body mass index, and VO₂peak (all P>0.05, Table 1). Hydration status, based on measurements of urine specific gravity, was similar prior to both calorimetry sessions and between groups (both P>0.05), averaging 1.014 ± 0.007 across sessions and groups.

Whole-body heat exchange

Baseline metabolic heat production, dry heat gain, net heat load, and evaporative heat loss were unaffected by heat acclimation and similar between groups before and after acclimation (all P>0.05), averaging 55 ± 7 W m⁻², -37 ± 9 W m⁻², 92 ± 10 W m⁻², and 76 ± 16 W m⁻² (respectively), across days and groups.
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The experimental paradigm used in this study ensured that metabolic heat production was identical between days ($P=0.62$) and between-groups ($P=0.65$), averaging $155 \pm 10 \text{ W m}^{-2}$ (low), $202 \pm 9 \text{ W m}^{-2}$ (moderate), and $253 \pm 11 \text{ W m}^{-2}$ (high) across days and groups, respectively. A treatment (i.e., heat acclimation) effect was observed on dry heat gain ($P=0.02$), albeit post-hoc comparisons yielded no differences in both groups (all $P>0.05$, Figure 1C). Moreover, dry heat gain was similar between groups before and after the heat acclimation treatment (main effect of group: $P=0.32$). A significant treatment effect was also observed for net heat load ($P=0.03$, Figure 1B), although the only difference was a greater net heat load during the moderate condition in the Control group post-heat acclimation ($P=0.01$). In contrast, there was no effect of group measured for net heat load ($P=0.13$). An acclimation effect was measured for evaporative heat loss (main effect of treatment: $P<0.01$, Figure 1B), with increases observed at the end of all three exercise-induced heat loads in both groups following heat acclimation (all $P<0.01$). An effect of group was also evident ($P<0.01$) such that the individuals with T2D exhibited lower evaporative heat loss at the end of the moderate ($P=0.04$) and high ($P=0.02$), but not low ($P=0.48$), intensity exercise relative to Control on day 0 (Figure 1B). However, these T2D-mediated impairments in evaporative heat loss were no longer apparent on day 8 (all $P>0.05$). Consequently, an effect of group ($P=0.04$) was observed for the magnitude of change in evaporative heat loss with heat acclimation such that it was greater for T2D relative to Control during the high heat load ($P=0.01$), but not at the moderate ($P=0.12$) and low ($P=0.87$) heat loads (Figure 2). Due to the improvements in evaporative heat loss, an effect of acclimation was measured for body heat storage ($P<0.01$, Figure 1D). Specifically, both groups stored a lower amount of heat during the moderate and high exercise conditions post-heat acclimation (all $P<0.01$), with no differences measured during the low condition (both $P<0.01$). Therefore, while an effect of group ($P<0.01$) revealed that body heat storage was greater during the moderate and high heat
Type 2 diabetes and short-term heat acclimation loads for T2D relative to Control on day 0 (both P<0.01), no significant between-group differences were evident on day 8 (all P>0.05).

**Time constants and amplitude of change in evaporative heat loss**

A significant treatment effect was observed for the time constant of evaporative heat loss (P=0.01, Table 2), with a significantly greater time constant measured at the high heat load in the T2D group on day 8 relative to day 0 (P=0.02). However, the time constant of evaporative heat loss did not differ between groups on days 0 and 8 (P=0.68). An acclimation effect was also observed for the amplitude of change in evaporative heat loss (P=0.01, Table 2) as a greater change was measured for the moderate (P=0.03) and high (P=0.01) heat loads in the T2D group, as well as for the high (P=0.02) heat load in the Control following the acclimation treatment. Furthermore, a group by time interaction (P=0.05, Table 2) was measured for the amplitude of change in evaporative heat loss such that it was lower during the moderate and high (both P<0.01), but not Low (P=0.83), exercise-induced heat loads for T2D relative to Control on day 0. However, the amplitude of evaporative heat loss was not different between groups on day 8 (all P>0.05).

**Rectal and mean skin temperatures, heart rate, and physiological strain index**

Baseline rectal and mean skin temperatures were unaffected by heat acclimation (both P>0.05) and similar between groups (all P>0.05), averaging 36.8 ± 0.4°C and 35.3 ± 0.4°C across days and groups, respectively. In contrast, baseline resting heart rate was greater for T2D compared to Control before (T2D: 80 ± 17 beats min⁻¹; Control: 64 ± 9 beats min⁻¹, P=0.02) and after (T2D: 77 ± 17 beats min⁻¹; Control: 62 ± 8 beats min⁻¹, P=0.03) heat acclimation. Further, the baseline heart rate response was significantly lowered by heat acclimation for Control (P=0.04), but not T2D (P=0.15).
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There was a significant acclimation effect for rectal temperature during exercise (P=0.05), albeit the only difference was a lower rectal temperature at the end of the high heat load for Control following heat acclimation (P=0.04, Table 3). In contrast, rectal temperature did not differ between groups on days 0 and 8 (P=0.16). Mean skin temperature was also affected by heat acclimation (P=0.03, Table 3). Specifically, mean skin temperature was decreased during the low (P=0.02) and high (P=0.05) exercise conditions in the T2D group following acclimation, with a trend observed during the moderate (P=0.07) condition. In comparison, the acclimation treatment did not affect mean skin temperature in the Control group (all P>0.05). Furthermore, there were no between-group differences in mean skin temperature on days 0 and 8 (P=0.06). There was a main effect of heat acclimation observed on percentage heart rate reserve (P<0.01, Table 3) in which a lower response was measured at the end of the moderate and high heat loads for Control (both all P<0.01), and at all heat loads for T2D following heat acclimation (all P<0.05). Additionally, percentage of heart rate reserve was different between groups (P<0.01, Table 3) with a greater level achieved at all heat loads for T2D relative to Control before heat acclimation (all P<0.05). However, no between-group differences in percentage of heart rate reserve were apparent following heat acclimation (all P>0.05). As a consequence of these differences, the physiological strain index changed as a function of heat acclimation (P=0.02, Table 3) as a lower response was measured at the end of the moderate (P=0.05) and high (P=0.04), but not low (P=0.43), heat loads in the individuals with T2D after heat acclimation. In contrast, a lower physiological strain index was only measured at the end of the high heat load in the Control group after the acclimation treatment (P=0.02), as no differences were observed at the low (P=0.90) and moderate (P=0.18) heat loads. Nevertheless, the physiological strain index did not differ between groups on days 0 and 8 (all P>0.05, Table 3).
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DISCUSSION

This study represents the first to use direct calorimetry to quantify changes in whole-body heat exchange following heat acclimation in older males with and without T2D. In line with our hypothesis, we showed that heat acclimation enhances whole-body evaporative heat loss during low-to-high exercise-induced heat loads performed in a hot, dry environment in older habitually active males with and without T2D, albeit the magnitude of change was greater in the individuals with T2D. As a result, the T2D-mediated impairments in evaporative heat loss and heat storage that were apparent during the moderate and high exercise-induced heat loads before heat acclimation were abolished following heat acclimation.

A novel finding of this study was that the heat acclimation treatment improved whole-body evaporative heat loss in habitually active older males with and without T2D during low–to–high intensity (47 to 60% \( \dot{V}O_{\text{peak}} \)) exercise performed in hot dry, conditions (Figure 1B). These observations are consistent with our previous work in young males (25), and are likely ascribed to an increase in the thermosensitivity (gain) of the sweating response in response to changes in mean body temperature as well as greater sweat gland output (43-46). However, since we have shown previously that habitually active, but not heat-acclimated, older men with T2D display impairments in evaporative heat loss at exercise-induced heat loads \( \geq 200 \text{ W m}^{-2} \) relative to their healthy counterparts (11), we hypothesized that the magnitude of adaptation following heat acclimation (i.e., ability to accommodate adaptation) would be greater due to this lowered physiological capacity to dissipate heat (i.e., pre-adaptation baseline). Consistent with that hypothesis, we showed that older males with T2D possessed a lower pre-adaptation baseline as indicated by a reduced evaporative heat loss at the moderate and high heat loads relative to their healthy counterparts prior to acclimation (Figure 1B). This was coupled with increases in evaporative heat loss of \(~7\%\), \(~10\%\), and \(~13\%\) during the low, moderate, and high heat loads in the
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T2D group, respectively, following acclimation, compared to only a ~6% improvement in evaporative heat loss at all heat loads in the Control group. Furthermore, while the time constant of evaporative heat loss was largely unaffected by heat acclimation in both groups (Table 2), the amplitude of change in evaporative heat loss at the moderate and high heat loads also increased to a greater extent for T2D (13 and 24%, respectively) compared to Control (4 and 12%, respectively). These novel outcomes demonstrate that older males with T2D display an enhanced responsiveness to heat acclimation relative to their age-matched healthy counterparts. Nonetheless, further research is required to determine whether it is strictly one’s pre-adaptation baseline or another mechanism associated with T2D that explains why older adults with T2D display a greater responsiveness to heat acclimation.

As a result of these greater improvements in heat dissipation (Figure 1B, Table 2), cumulative body heat storage over the three exercise bouts, which was 25% greater in those with T2D prior to heat acclimation, no longer differed significantly between groups following heat acclimation (Figure 1D). This unique and important outcome indicates that T2D-mediated impairments in whole-body heat dissipation are abolished by short-term moderate-intensity exercise training in the heat. Therefore, heat-acclimated males with T2D may be able to perform exercise safely in the heat to manage their disease, a practice that is currently not advocated by Diabetes Canada and the American Diabetes Association (29, 30). This is because adults with T2D may be at greater risk of heat-related illnesses and/or death relative to the general population due to their impaired capacity to dissipate heat during exercise in the heat (10, 11). However, our findings demonstrate that habitually active older males with well-controlled T2D essentially respond like healthy habitually active older males following short-term heat acclimation. This scenario is still problematic for adults with and without T2D as they are still at greater risk relative to young adults during exercise in the heat due to age-related impairments in the body’s capacity to
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dissipate heat (47-49). Future work is therefore necessary to determine how these age-related impairments in heat dissipation may be altered by short-term heat acclimation.

The heat acclimation treatment also exhibited a differential effect on cardiovascular strain in older adults with and without T2D, such that the percentage of heart rate reserve achieved across all three exercise bouts was reduced by ~22% in those with T2D, compared to a ~16% reduction in the nondiabetic group (Table 3). This greater magnitude of reduction in the T2D group mitigated the differences in heart rate reserve that were evident between groups prior to heat acclimation (Table 3). These findings are consistent with extensive research showing that improvements in cardiovascular stability occur in the early stages of heat exposure to stabilize mean arterial and venous blood pressures (45, 50). The mechanisms responsible for this reduction in cardiovascular strain have been associated with an expansion of plasma volume, an increase in venous tone from cutaneous and non-cutaneous vascular beds, a reduction in sympathetic activation of the heart, improved evaporative cooling and redistribution of blood volume, as well as a reduction in core temperature (26). Therefore, it is possible that short-term heat acclimation may induce the same benefits as chronic resting heat exposure (i.e., 15 min exposure in sauna at 80-100°C, 4-7 times/weekly; hot water immersion at 40°C for up to 8 weeks) on hemodynamics, vascular and autonomic function, and exercise capacity in young (aged 18 to 30 years) and older adults (aged 60-70 years) (51, 52), as well as those with congestive heart failure (52). Ultimately, regular heat exposure, either from exercise and/or resting in the heat, may serve as an important treatment method to mitigate impairments in vascular and autonomic function, cardiac output, and blood pressure regulation in older adults with T2D (28).

It is well recognized that heat acclimation lowers core temperature during exercise (26), primarily because of a 0.3 to 0.4°C reduction in resting core temperature. However, the heat acclimation treatment in this study generally did not affect rectal temperature at rest (mean non-significant decrease
Type 2 diabetes and short-term heat acclimation of ~0.1°C across groups) or during exercise in either T2D or Control (Table 3). This was surprising since we observed marked reductions in body heat storage measured by direct calorimetry in both groups (Figure 1D). This inconsistency is likely explained by the fact that core temperature does not always provide an accurate assessment of changes in body heat storage during exercise in the heat (39). The current results therefore support this notion, yet confirm that short-term heat acclimation reduces whole-body heat storage during exercise in older adults with and without T2D, irrespective of whether this is represented in the change in core temperature. Therefore, the change in body heat storage may be a better indicator of thermal adaptation relative to changes in core temperature alone. Furthermore, the physiological strain index, which considers the circulatory (i.e., heart rate) and thermal (i.e., rectal temperature) components to the overall physiological strain, was reduced by ~17% in both groups by the end of the third exercise bout following heat acclimation (Table 3). However, since rectal temperature was unaffected by the acclimation treatment, the reduction in circulatory strain was the major component that contributed to the overall decrease in physiological strain with heat acclimation. Therefore, the likelihood of adverse cardiovascular events during exercise in the heat may be reduced following heat acclimation in habitually active adults with and without T2D.

**Considerations**

The individuals with T2D included in this study were habitually active, had good diabetes control (i.e., level of glycemic control, HbA1c), and were free of T2D-related complications (i.e., peripheral and/or autonomic neuropathy, and others) and comorbidities (i.e., chronic hypertension, cardiovascular disease, obesity, others). It is possible however, that these factors may exacerbate impairments in whole-body heat dissipation in non-heat acclimated adults with T2D, especially since they have been associated with greater reductions in sweating and skin blood flow (28). As a result of this potentially lower physiological capacity to dissipate heat; older adults with T2D who are more
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sedentary and/or have T2D-related complications and comorbidities may possess an even lower pre-adaptation baseline level relative to their habitually active, well-controlled counterparts. In turn, this may lead to a greater accommodation reserve and consequently a greater capacity to adapt and respond to a given adaptation stimulus. However, there is also a possibility that one’s capacity to adapt to a given heat acclimation stimulus may be reduced by such complications, albeit this is currently unknown. Future studies are therefore warranted to determine the extent to which whole-body heat exchange may be altered in more sedentary older adults with T2D, who may or may not have complications and/or comorbidities, and whether short-term heat acclimation can provide similar or even greater thermoregulatory benefits. However, it is important to note that these individuals may not have the capacity to exercise. As such, passive heat acclimation/therapy may be a better option to improve overall thermoregulatory and cardiovascular function in this heat vulnerable population (51, 52).

The heat acclimation protocol used in this study consisted of exposure to dry heat, lasted only 7 days, and the assessment of whole-body heat exchange was performed in an environment that favoured the complete evaporation of sweat (high air mass flow combined to low absolute humidity). Therefore, it is essential that future studies determine the extent to which whole-body heat exchange and heat storage may be altered by longer duration protocols (>7 days) as well as in more humid conditions in older adults with and without T2D. This is important since the physiological adaptations between hot-dry and hot-humid conditions differs markedly (26), with the latter relying more heavily on decreasing metabolic heat production (i.e., increases in metabolic efficiency) and/or reducing the rate of dry heat gain (i.e., increase in skin blood flow and skin temperature) from the environment to reduce thermal and cardiovascular strain during exercise (53). Understanding the key physiological differences between environments is important as hot-humid conditions are regularly encountered around the world (e.g.,
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Europe, North America, South America, Africa) and in habitually demanding occupations (e.g., mining, electric utilities, others).

Perspectives and significance

The outcomes from this study have important implications regarding physical activity recommendations in adults with T2D. At present, Diabetes Canada and the American Diabetes Association recommends that adults with T2D avoid strenuous, prolonged, exercise in the heat due to their reduced capacity to dissipate heat (29, 30). Our findings demonstrate that short-term moderate-intensity exercise training, when performed in the heat, provides an effective way for older males with well-controlled T2D to improve their capacity to dissipate heat. However, performing this type of protocol, without adequate supervision, may prove to be dangerous for adults with T2D due to the rapid and sustained elevations in core temperature. It is possible that other methods, such as passive heat therapy (i.e., sauna bathing and/or water immersion), may be equally as effective at enhancing whole-body heat dissipation without requiring such strenuous physical efforts to be performed to induce adaptation. While future work is essential to precisely determine the extent to which passive heat exposure/therapy can improve whole-body heat dissipation during exercise in the heat in adults with T2D, it has been reported to be less effective than exercise in the heat, providing only partial thermoregulatory adaption (54). However, sauna bathing (80–100°C; hot tub at 40°C/15 min, three times per week for 3 months) is an interesting area of future research as it has been shown to provide similar benefits as exercise on overall metabolic health (i.e., reductions in fasting glycemia, glycated hemoglobin, and adiposity) in adults with T2D (30, 55-57). Furthermore, studies are required to determine the extent to which everyday physical activity/work in warm (rather than artificially-induced acclimation in a controlled setting) and temperate environmental conditions may improve thermoregulatory function in individuals with T2D.
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In the context of occupational health, our findings are critical for the establishment of heat exposure guidelines. Currently, the American Conference of Governmental and Industrial Hygienists (ACGIH®) Threshold Limit Values (TLV® guidelines) are the most recommended for work in the heat as they consist of work-rest allocations designed to ensure a stable core temperature that does not surpass 38°C (58). While these guidelines consider the acclimatization state of the individual, they do not consider other individual factors such as age, sex, morphology, aerobic fitness, and health status (i.e., T2D and other chronic disease), all of which can affect an individual’s capacity to dissipate heat (10, 47, 49, 58-63). Our findings reinforce the fact that T2D should be independently considered in non-heat acclimated older adults, whereas this may not be required once an individual becomes acclimated to the heat. However, given that the exercise bouts in this study were of short duration, it is essential that future studies examine how our results may be altered during more prolonged work in the heat. Furthermore, it is currently unknown how long the improvements in heat dissipation are maintained in older adults with and without T2D when the heat stimulus is absent, although the current recommendation is that 1 day of heat acclimation should be performed for every 2 days that are spent away from the heat (25, 26). Nevertheless, this recommendation is based on artificially-induced adaptation (i.e., daily exercise performed in a controlled thermal chamber), therefore it remains to be determined how naturally-induced adaptations (i.e., heat acclimatization) that occur through exercise/work in hot environments and/or due to seasonal heat exposure may alter this recommendation (26).
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CONCLUSIONS

In summary, we showed for the first time that short-term heat acclimation improves whole-body evaporative heat loss and reduces cardiovascular strain during low-to-high intensity exercise performed in a hot, dry environment in habitually active older males with and without T2D, with the magnitude of those improvements being greater in those with T2D. As a result, the impairments in evaporative heat loss and greater cardiovascular strain observed in older adults with T2D during exercise in the heat prior to acclimation were abolished following acclimation.

ACKNOWLEDGMENTS

The authors are indebted to the study participants for the success of this study. The authors would also like to thank all members of the Human and Environmental Physiology Research Unit who helped with data collection as well as participant recruitment.

GRANTS

The study was conducted at the Human and Environmental Physiology Research Unit (HEPRU). This study was funded by the Canadian Institutes of Health Research as well as the Ontario Ministry of Labour (all funds held by G. P. Kenny). G. P. Kenny was supported by a University of Ottawa Research Chair Award. M. P. Poirier was supported by Natural Sciences and Engineering Research Council of Canada Alexander Graham Bell Scholarship (CGS-D), HEPRU, as well as the University of Ottawa. S.R. Notley was supported by a Postdoctoral Fellowship from HEPRU. A.W. D’Souza was supported by a Queen Elizabeth II Graduate Scholarship in Science and Technology. R.J. Sigal was supported by a Health Senior Scholar award from Alberta Innovates-Health Solutions.
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AUTHOR CONTRIBUTIONS

M.P.P and G.P.K conceptualized and designed the research. M.P.P., S.R.N. and A.D. performed experiments. M.P.P. performed data analysis. All authors interpreted the experimental results. M.P.P. prepared figures and drafted manuscript. All authors edited and revised the manuscript. All authors approved the final version of the manuscript.
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REFERENCES


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Table 1. Participant characteristics

<table>
<thead>
<tr>
<th></th>
<th>Age (years)</th>
<th>Height (cm)</th>
<th>Mass (kg)</th>
<th>BSA (m²)</th>
<th>Body fat (%)</th>
<th>BMI (kg·m⁻²)</th>
<th>VO₂peak (mL·kg⁻¹·min⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T2D</td>
<td>58 ±5</td>
<td>176 ± 3</td>
<td>85.5 ± 13.4</td>
<td>2.0 ± 0.1</td>
<td>25.8 ± 4.7</td>
<td>25.7 ± 2.0</td>
<td>32.5 ± 7.4</td>
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<tr>
<td>Control</td>
<td>61 ± 6</td>
<td>174 ± 4</td>
<td>77.5 ± 5.2</td>
<td>1.9 ± 0.1</td>
<td>23.2 ± 4.0</td>
<td>27.6 ± 4.3</td>
<td>37.4 ± 5.2</td>
</tr>
</tbody>
</table>

Values are mean ± SD. T2D, type 2 diabetes. BSA, body surface area. BMI, body mass index. VO₂peak, peak aerobic power. Body fat % was assessed using the hydrostatic weighing technique. VO₂peak was determined during a maximal incremental semi-recumbent cycling protocol. There were no significant differences between groups, all P>0.05.
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Table 2. Time constants (τ) and amplitudes of whole-body evaporative heat loss in older habitually active males with (T2D, n=8) and without (Control, n=10) T2D during three 30-min bouts of cycling at increasing fixed rates of metabolic heat production of 150 (low), 200 (moderate), and 250 (high) W m$^{-2}$, in a hot, dry environment (40°C, ~15% relative humidity) prior to (day 0) and following (day 8) 7 days of traditional heat acclimation (90 min of exercise at 50% of VO$_{2peak}$).

<table>
<thead>
<tr>
<th>Groups</th>
<th>Low</th>
<th>Moderate</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 0</td>
<td>Day 8</td>
<td>Day 0</td>
</tr>
<tr>
<td>T2D</td>
<td>9 ± 5</td>
<td>14 ± 5</td>
<td>8 ± 3</td>
</tr>
<tr>
<td>Control</td>
<td>10 ± 7</td>
<td>12 ± 5</td>
<td>7 ± 2</td>
</tr>
<tr>
<td>T2D</td>
<td>124 ± 41</td>
<td>134 ± 36</td>
<td>116 ± 22†</td>
</tr>
<tr>
<td>Control</td>
<td>127 ± 24</td>
<td>145 ± 30</td>
<td>147 ± 18</td>
</tr>
</tbody>
</table>

Values are mean ± SD. Tau (τ) indicates the time constant for evaporative heat loss to reach 63.2% of the total amplitude as determined via exponential one-phase association nonlinear regression analysis. (*) Significantly different from day 0, P<0.05; (†) Significantly different from Control, P<0.05.
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Table 3. Rectal and mean skin temperatures, heart rate, percentage heart rate reserve, and the physiological strain index in older habitually active males with (T2D, n=8) and without (Control, n=10) T2D during three 30-min bouts of cycling at increasing fixed rates of metabolic heat production of 150 (low), 200 (moderate), and 250 (high) W m\(^{-2}\), in a hot, dry environment (40°C, ~15% relative humidity) prior to (day 0) and following (day 8) 7 days of heat acclimation (90 min of exercise at 50% of \(\dot{V}O_{2\text{peak}}\)).

<table>
<thead>
<tr>
<th></th>
<th>Low</th>
<th>Moderate</th>
<th>High</th>
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<tbody>
<tr>
<td></td>
<td>Day 0</td>
<td>Day 8</td>
<td>Day 0</td>
</tr>
<tr>
<td><strong>Rectal temperature, °C</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2D</td>
<td>37.3 ± 0.3</td>
<td>37.3 ± 0.3</td>
<td>37.7 ± 0.3</td>
</tr>
<tr>
<td>Control</td>
<td>37.2 ± 0.5</td>
<td>37.1 ± 0.3</td>
<td>37.6 ± 0.4</td>
</tr>
<tr>
<td><strong>Mean skin temperature, °C</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2D</td>
<td>35.8 ± 0.4</td>
<td>35.6 ± 0.3*</td>
<td>35.9 ± 0.4</td>
</tr>
<tr>
<td>Control</td>
<td>35.6 ± 0.4</td>
<td>35.3 ± 0.5</td>
<td>35.7 ± 0.6</td>
</tr>
<tr>
<td><strong>Heart rate reserve, %</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2D</td>
<td>19 ± 10</td>
<td>10 ± 3*</td>
<td>62 ± 16†</td>
</tr>
<tr>
<td>Control</td>
<td>13 ± 6</td>
<td>12 ± 7</td>
<td>49 ± 10</td>
</tr>
<tr>
<td><strong>Physiological strain index</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2D</td>
<td>1.2 ± 0.4</td>
<td>1.0 ± 0.2</td>
<td>2.1 ± 0.5</td>
</tr>
<tr>
<td>Control</td>
<td>1.0 ± 0.4</td>
<td>1.0 ± 0.5</td>
<td>1.9 ± 0.6</td>
</tr>
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</table>

Values are mean ± SD. (*) Significantly different from Day 0, P<0.05; (†) Significantly different from Control, P<0.05.
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Figure 1. Change in net heat load (panel A), evaporative heat loss (panel B), dry heat exchange (panel C), and body heat storage (panel D) in older habitually active males with (T2D, n=8) and without (Control, n=10) T2D during three 30-min bouts of cycling at increasing fixed rates of metabolic heat production of 150 (low), 200 (moderate), and 250 (high) W m⁻², in a hot, dry environment (40°C, ~15% relative humidity) prior to (day 0) and following (day 8) 7 days of heat acclimation (90 min of exercise at 50% of \( \dot{V}O_{2\text{peak}} \)). Values are mean ± SD. (*) Significantly different from Day 0, P<0.05; (†) Significantly different from Control, P<0.05.
Figure 2. The percent change in whole-body evaporative heat loss in older habitually active males with (T2D, n=8) and without (Control, n=10) T2D during three 30-min bouts of cycling at increasing fixed rates of metabolic heat production of 150 (low), 200 (moderate), and 250 (high) W m⁻², in a hot, dry environment (40°C, ~15% relative humidity) following 7 days of traditional heat acclimation (90 min of exercise at 50% of \( \dot{\text{VO}}_{2\text{peak}} \)). Values are mean ± SD. (†) Significantly different from Control, P<0.05.
CHAPTER 4

THESIS DISCUSSION
4.1. Thesis discussion

The primary objective of the current thesis was to examine the effects of T2D on the body’s physiological capacity to dissipate heat in habitually active older adults at rest and during exercise in the heat. The first study established that habitually active older adults with T2D do not display impairments in whole-body heat loss, and therefore experience similar levels of thermal and cardiovascular strain, throughout a brief 3-hour passive exposure to extreme heat relative to their age-matched non-diabetic counterparts. The second study allowed us to show, for the first time, that T2D-mediated impairments in whole-body evaporative heat loss are indeed heat load-dependent, such that they become evident at exercise-induced heat loads ≥200 W m⁻² in habitually active older males with well-controlled T2D. Importantly, the magnitude of those differences became greater with increasing exercise intensity when performed in the heat. These impairments in evaporative heat loss capacity led to a greater change in body heat storage, core temperature, heart rate, and physiological strain index in those with T2D compared to the healthy older males. The third study demonstrated that short-term heat acclimation can enhance whole-body evaporative heat loss and reduce cardiovascular strain during exercise-induced heat loads ranging from 150 to 250 W m⁻² when performed in a hot, dry environment, in habitually active older males with and without T2D. However, the magnitude of those improvements was distinctly greater in those with T2D, which abolished the impairments in evaporative heat loss/body heat storage and cardiovascular stain observed in non-heat acclimated habitually active older males with T2D.

The first study was specifically designed to determine whether habitually active older adults have an impaired capacity to dissipate heat during a 3-hour exposure to extreme heat relative to their non-diabetic counterparts. In this context, two previous
studies had assessed local heat loss and core temperature responses in older adults with T2D during environmental heat exposure (~42°C) (28, 130). While they demonstrated a reduction in maximal sweating and skin blood flow responses, as well as a greater rise in core temperature, this exposure was relatively short (30 min) and did not provide an accurate insight into potential T2D-mediated differences in whole-body heat exchange (evaporative and dry) and heat storage during a more prolonged exposure to extreme heat. Therefore, we employed direct calorimetry, which allows the examination of time-dependent changes in whole-body dry and evaporative heat exchange and the resulting changes in body heat storage, to assess whether whole-body heat dissipation and the resulting changes in heat storage would be impaired in habitually active older adults with T2D during a 3-hour passive heat exposure (44°C and 30% relative humidity). Since T2D has also been associated with marked impairments in cardiovascular function (i.e., autonomic and vascular function, cardiac output, blood pressure control, etc.) (30, 121, 126-128, 131-136), we examined whether individuals with T2D would experience greater cardiovascular strain as a result of potentially greater levels of hyperthermia during passive heat exposure. In contrast to our hypothesis, we showed that habitually active older adults with T2D did not exhibit an impaired capacity to dissipate heat during passive exposure to extreme heat relative to healthy older adults without T2D, which led to a similar amount of heat stored between both groups. This similar change in body heat storage was paralleled by identical increases in core temperature and cardiovascular strain (i.e., heart rate, cardiac output, blood pressure, limb perfusion). Since a previous study reported clear T2D-mediated impairments in whole-body evaporative heat loss during exercise in a warm environment (41), our findings led us to believe that impairments in the body’s ability to
dissipate heat in habitually active adults with T2D may only be evident above a specific level of heat stress.

Prior to this thesis, only one study to our knowledge had examined the extent to which T2D-mediated reductions in regional (i.e., torso, limbs and/or extremities) skin blood flow and sweating may translate into impairments in whole-body heat exchange during exercise in the heat (41). In this study, sedentary older adults with well-controlled T2D had a marked reduction in whole-body evaporative heat loss (and therefore whole-body sweat rate) during a single bout of light-to-moderate intensity exercise in a warm environment (30°C) that led to a body heat storage 1.6-times greater relative to their sedentary non-diabetic counterparts (41). However, it remained unclear whether this reduced whole-body evaporative heat loss capacity would also occur in habitually active older adults with a greater aerobic fitness level. In fact, a recent study reported that performing regular physical activity and maintaining a high level of aerobic fitness (as defined by \( \dot{V}O_{2\text{peak}} \)) can delay age-related impairments in heat dissipation in middle-aged males (7). Furthermore, since our previous assessment of whole-body heat exchange was limited to a single exercise-induced heat load (metabolic heat production of 185 W m\(^{-2}\)), it remained unclear whether impairments in whole-body heat evaporative heat loss, if observed, would become greater with increasing levels of heat stress.

The second study of this thesis was designed to examine the effect of T2D on whole-body heat exchange during exercise at progressively greater fixed rates of metabolic heat production (150, 200, and 250 W m\(^{-2}\)) in hot, dry conditions (40°C and 15% relative humidity) in habitually active older males. With our unique experimental design, we showed for the first time that habitually active older males with T2D also have a marked reduction in whole-body evaporative heat loss compared to their nondiabetic counterparts,
albeit this impairment only occurred at exercise-induced heat loads ≥200 W.m⁻², with the magnitude of that impairment becoming greater with each increasing heat load. This reduced evaporative heat loss capacity was characterized by a lower increase of the response as well as a lower plateau level achieved. As a result of this heat load-dependent impairment in heat dissipation, the individuals with T2D stored increasingly more heat over each exercise bout, which led to 27% more heat stored over the three exercise bouts. This greater heat storage was paralleled by a more pronounced increase in core temperature, heart rate, and physiological strain index across the exercise protocol. These observations confirm that habitually active older males with T2D have an impaired capacity to dissipate heat compared to their habitually active non-diabetic counterparts matched for age, physical characteristics, and aerobic fitness. Altogether, our findings combined to those by Kenny et al. (41), reinforce the notion that both sedentary and habitually active older individuals with well-controlled T2D should exercise caution when performing moderate-to-high-intensity exercise (i.e., walking, jogging, cycling) or physical work in the heat common to many occupations (i.e., electrical utilities, firefighting, mining, farming, and others). Ultimately, their impaired ability to thermoregulate may exacerbate the risk of heat-related illness (i.e., heat exhaustion, heat stroke, and others) and/or death, particularly with increases in heat load (as defined by the combination of environmental conditions and rate of metabolic heat production).

Physical activity has long been recognized as fundamentally important in the management of T2D due to its ability to enhance glycemic control (i.e., fasting glycemia, HbA1c), improve overall cardiovascular function (i.e., blood pressure regulation, autonomic and vascular function, etc.), prevent disease-related complications (i.e., neuropathy), as well as increase physical capacity in adults with T2D (42, 43). However,
Diabetes Canada and the American Diabetes Association currently advocate that individuals with T2D should avoid strenuous, prolonged, physical exertion in the heat due to their reduced capacity to dissipate heat and greater overall risk of adverse heat-related health events (25, 26, 40). These recommendations are supported by the findings from the second study as well as those from our previous work in sedentary adults with T2D (41). Nonetheless, no study to our knowledge has specifically assessed whether T2D-mediated impairments in heat dissipation may be altered by regular heat exposure (i.e., heat acclimation), and whether the risk of heat-related injury (and death) may be reduced by such interventions.

The third study of this thesis was therefore designed to examine if short-term heat acclimation can mitigate T2D-mediated impairments in whole-body evaporative heat loss in habitually active older males. To do so, we used direct calorimetry to assess whole-body evaporative heat loss during the same incremental exercise protocol as the second thesis study, which was performed prior to and following 7 days of traditional heat acclimation (90 min daily cycling at 50% of $\dot{V}O_{2\text{peak}}$ at 40°C and 20% relative humidity) in habitually active older males with and without T2D. Consistent with our findings from the second thesis study, the individuals with T2D had a lower pre-adaptation baseline due to a reduced evaporative heat loss and greater body heat storage during moderate-to-high intensity exercise (47 to 60% $\dot{V}O_{2\text{peak}}$) relative to their to their non-diabetic counterparts before heat acclimation. As expected, heat acclimation enhanced evaporative heat loss in both groups during low–to–high intensity (35 to 60% $\dot{V}O_{2\text{peak}}$) exercise performed in dry heat, albeit the magnitude of improvement was greater in the individuals with T2D. Specifically, heat acclimation increased evaporative heat loss by as much as ~13% in the individuals with T2D, whereas the maximal increase was measured to be ~6% in the healthy group. These
greater improvements in evaporative heat loss were also paralleled by a greater reduction in percentage of heart rate reserve in those with T2D following heat acclimation. Therefore, our key findings of this study demonstrate that habitually active older males with T2D display an enhanced responsiveness to short-term heat acclimation relative to their matched non-diabetic counterparts. As a result, the T2D-mediated impairments in evaporative heat loss, heat storage, and cardiovascular strain that were evident before heat acclimation were eliminated following heat acclimation. These findings support the notion that the degree of adaptation in sweating (and therefore evaporative heat loss capacity) is reliant on one’s accommodation reserve, which is defined by the pre-adaptation baseline (i.e., starting point) and the genetically pre-determined physiological maximum (52). Therefore, it is possible that the greater magnitude of adaptation in the T2D group may have, in part, been due to their reduced ability to dissipate heat prior to the heat acclimation treatment and therefore greater accommodation reserve (and therefore adaptive capacity).

4.1.2. Implications

The results from the current thesis have important implications for heat advisories during heat waves. The lack of discernable differences in thermal and cardiovascular strain between habitually active older adults with and without T2D during passive exposure to extreme heat implies that both can now be considered within the same population group during the initial hours of a heat wave. However, further research is warranted to determine if an extended exposure period (>3 hours) would alter the similar pattern of response observed in the current thesis and/or whether our outcomes would remain intact in more humid heat common to many places around the world (e. g., Europe, North America, South America, Asia, and Africa). This knowledge is essential to the development of all-
encompassing guidelines and policies related to the management of vulnerable populations in extreme heat conditions. Since the incidence and severity of heat waves is predicted to increase significantly in coming years (147, 148), this information is necessary to minimize heat-related morbidity and mortality during extreme heat events, especially since the mean age of the population and the incidence and prevalence of T2D is on the rise (60, 149).

Another important implication of this thesis relates to the physical activity recommendations for the management of T2D. It is well acknowledged that physical activity is paramount to the management of T2D due to its numerous cardiometabolic health benefits (i.e., reduction in fasting glycemia and HbA1c, improved cardiovascular function, weight loss and reduction in body fat, enhanced physical capacity, and others) (42, 43). However, current guidelines from Diabetes Canada and the American Diabetes Association recommend that individuals with T2D avoid performing vigorous (40 to 70% of \( \dot{V}O_{2\text{peak}} \)) physical activity/work in the heat due to their reduced capacity to dissipate heat (42, 43). The results from the second and third studies in this thesis, as well as from our previous work (41), reaffirmed that these recommendations are necessary as non-heat acclimated sedentary and habitually active individuals with T2D do experience important reductions in heat dissipation during moderate-to-high intensity exercise in the heat, which exacerbates the level of hyperthermia (i.e., body heat storage and core temperature) and cardiovascular strain (i.e., heart rate) they experience relative to their sedentary and habitually active counterparts, outcomes that become more pronounced with increasing heat loads (and therefore exercise/work intensity). Due to this increased physiological strain, disease-related symptoms could be exacerbated in individuals with T2D as well as greater levels of dehydration due to hyperglycemia and/or medication use (24), all of which can increase the possibility of heat-related injury and/or death.
While physical activity in the heat is discouraged in non-heat acclimated adults with T2D (42, 43), the findings from the third thesis study demonstrated that the level of thermal and cardiovascular strain can be mitigated by short-term heat acclimation as the individuals with T2D were able to offset the impairments in whole-body evaporative heat loss following heat acclimation. However, performing this type of protocol, without adequate supervision, may be dangerous for these heat vulnerable individuals due to the fast and constant elevations in core temperature. It is possible that other intervention methods, such as passive heat therapy (i.e., sauna bathing and/or water immersion), may provide similar thermoregulatory benefits as exercise in the heat (150, 151), without requiring such a vigorous physical effort to induce adaptation. In fact, chronic passive heat therapy (sauna bathing at 80–100°C; hot tub at 40°C/15 min, three times per week for 3 months) has been shown to provide similar benefits as exercise on some aspects of metabolic health (i.e., reductions in fasting glycemia, glycated hemoglobin, and adiposity) in adults with T2D (43, 152-154). This type of intervention is particularly attractive for individuals with limited mobility, contraindications for exercise and/or with limited exercise capacity. Within such populations, individuals often cannot exercise at high enough intensity to promote thermoregulatory and cardiovascular benefits and adherence is difficult to maintain over time. Furthermore, additional work is required to examine how everyday passive exposure and/or low-to-high intensity physical activity/work in warm (rather than artificially-induced in a laboratory setting) and temperate environments may enhance thermoregulatory capacity in adults with T2D.

An important area of research that is necessary based on the results of the current thesis is to examine if they may have practical implications for everyday work in the heat. Currently, heat exposure guidelines, such as the American Conference of Governmental
and Industrial Hygienists (ACGIH®) Threshold Limit Values (TLV® guidelines) (155), recommend work-to-rest ratios based on a combination of environmental conditions (i.e., Wet Bulb Globe Temperature) and rates of metabolic heat production in order to ensure a stable core temperature that does not exceed 38°C. The results from the second thesis study, specifically the lower evaporative heat loss in non-heat acclimated males with T2D relative to the heat load, propose that the near maximal evaporative capacity is lower in individuals with T2D. As a result, an uncompensable heat stress condition would happen at a relatively lower heat load in adults with T2D compared to adults without T2D. Since current heat exposure guidelines do not independently consider T2D, similar work-to-rest allocations are recommended to adults with and without T2D to avoid possibly dangerous elevations in core temperature. However, it is likely that these recommendations underestimate the level of heat stress in those with T2D, especially at higher heat loads (due to increases in physical work performed), which could surpass the maximal (or near maximal) evaporative capacity of individuals with T2D, which would not be the case for those without T2D. In such situations, adults with T2D would experience greater increases in core temperature, which if left unchecked, would continue to rise as physical activity/work is sustained. Therefore, future work is required to determine the extent to which T2D-mediated impairments in evaporative heat loss may alter the core temperature response for specific work-to-rest regimens relative to healthy nondiabetic adults, and how this response may be further affected by heat acclimation.

4.1.2. Limitations

All participants who participated in the studies included in this thesis were habitually active and aged between 50 and 75 years (older adults). Therefore, the results of
this thesis are not applicable to individuals who are sedentary, children, adolescents (<18 years), young and middle-aged adults (18 to 50 years) and the elderly (aged 75 years and above). While two female participants were included in the first thesis study, only males participated in both exercise studies as sex has been shown to independently modulate whole-body heat exchange in a heat load dependent manner (metabolic heat load ≥300 W m⁻²) during exercise in the heat (47). Therefore, the results of this thesis are not applicable to older females with T2D, albeit future work should aim to examine the extent to which T2D may influence whole-body heat exchange in women during passive and exercise-induced heat stress. Furthermore, the individuals with T2D who participated in this thesis had been diagnosed for a minimum of 5 years, were generally healthy as evidenced by relatively good glycemic control (had an HbA₁c ≤9.0%) and had not been previously clinically diagnosed with any diabetes-related complications (i.e., neuropathy, nephropathy, retinopathy, etc.). As such, the results of this thesis are not applicable to individuals who have had T2D for less than 5 years, who have poor glycemic control, and/or have T2D-related complications. That being said, an important avenue of future research that is warranted is to examine the extent to which these factors may alter the outcomes of the current thesis, especially since longer duration diabetes, poor glycemic control, as well as T2D-related complications and comorbidities have been associated to a greater risk of heat-related injury and/or death during heat stress (24).
4.2. Thesis conclusions

Collectively, the findings from the current thesis greatly advance our understanding of T2D-mediated changes in thermoregulatory function from a whole-body perspective. Overall, the results show that habitually active older adults with T2D do not exhibit a reduced capacity to dissipate heat during passive heat exposure compared to habitually active non-diabetic older adults. However, T2D does impair evaporative heat loss above a specific exercise-induced heat load threshold, with the magnitude of that impairment becoming greater with increases in exercise intensity. These outcomes indicate that habitually active older males with T2D may be at greater risk of heat-related injury (e.g., heat exhaustion, heat syncope, heat stroke), work-related injuries (i.e., due to increases in hyperthermia-induced fatigue), and/or death, compared to healthy habitually active older males, especially during more strenuous work or physical activity in hot, dry environments. However, short-term acclimation abolished the T2D-mediated reductions in whole-body evaporative heat loss, which could ultimately reduce the chance of adverse health outcomes when physical activity/work is performed in the heat.
CHAPTER 6

REFERENCES
6.1. References


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