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Body temperature regulation in diabetes

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ABSTRACT

The effects of type 1 and type 2 diabetes on the body's physiological response to thermal stress is a relatively new topic in research. Diabetes tends to place individuals at greater risk for heat-related illness during heat waves and physical activity due to an impaired capacity to dissipate heat. Specifically, individuals with diabetes have been reported to have lower skin blood flow and sweating responses during heat exposure and this can have important consequences on cardiovascular regulation and glycemic control. Those who are particularly vulnerable include individuals with poor glycemic control and who are affected by diabetes-related complications. On the other hand, good glycemic control and maintenance of aerobic fitness can often delay the diabetes-related complications and possibly the impairments in heat loss. Despite this, it is alarming to note the lack of information regarding diabetes and heat stress given the vulnerability of this population. In contrast, few studies have examined the effects of cold exposure on individuals with diabetes with the exception of its therapeutic potential, particularly for type 2 diabetes. This review summarizes the current state of knowledge regarding the impact of diabetes on heat and cold exposure with respect to the core temperature regulation, cardiovascular adjustments and glycemic control while also considering the beneficial effects of maintaining aerobic fitness.

Introduction

Diabetes mellitus, commonly known as diabetes, refers to a group of metabolic disorders which are associated with an impaired ability to regulate glycemia. Type 1 and type 2 diabetes are the most prevalent forms of the disease representing ~10 and ~90% of cases, respectively.[1] Type 1 diabetes was formerly known as juvenile diabetes due to its common presentation in children and adolescents, and is characterized by the endocrine pancreas ceasing to produce insulin following the immune-mediated destruction of β-islet cells.[2] Therefore, management of type 1 diabetes always requires exogenous delivery of insulin. Although the causes of type 1 diabetes remain to be elucidated, it is probably caused by a combination of genetic predisposition (with >40 loci known to affect susceptibility)[3] and various environmental factors including stress and viruses.[4] On the other hand, type 2 diabetes is most often diagnosed in adults and typically involves a combination of insulin resistance and relative (rather than absolute) deficiency of insulin.[5] While the causes of type 2 diabetes are also incompletely understood, a plethora of studies have found associations with excessive abdominal adiposity,[6] sedentary lifestyle, and poor dietary habits[7] along with genetic factors. In contrast to type 1, type 2 diabetes may be treated in several ways including non-insulin pharmaceuticals, lifestyle modifications as well as exogenous insulin administration.

Diabetes is becoming a worldwide public health issue, with the global prevalence in 2014 estimated at 9% among adults.[8] By 2035, the International Diabetes

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Federation has projected a prevalence of 592 million cases with an additional ~175 million going undiagnosed.[9] In North America alone, ~7% (2.5 million) of Canadian adults reported having diabetes in 2009[10] along with ~9% (29.1 million) of Americans in 2012.[11] The economic burden of diabetes is estimated to be $245 billion in direct and indirect costs in the United States alone.[12] Much of the burden of diabetes comes from the disabling and common complications that are associated with the disease, many of which can be subcategorized into macro- and microvascular complications.[13] For example, young adults with type 1 diabetes have 10-times the risk for cardiovascular events relative to their healthy counterparts[14] and the most common cause of death in individuals with type 2 diabetes is cardiovascular-related.[15]

More recently, diabetes has been linked to impairments in temperature regulation during exposure to thermal stress. While it remains a new area of investigation, the topic of diabetes and heat exposure has gained particular interest in light of climate change and the increasing prevalence of heat waves.[16-18] Individuals with types 1 and 2 diabetes are reported to be particularly vulnerable during extreme heat events as they account for a disproportionate number of hospitalizations and deaths.[19] The most recently published physical activity recommendations for individuals with diabetes highlight their susceptibility to adverse heat-related events and caution against physical exertion in the heat.[20] In contrast, while some have suggested individuals with diabetes to be potentially more susceptible to the consequences cold stress,[21] most research in this area has suggested possible therapeutic effects of cold exposure for individuals with type 2 diabetes.[22-24]

Thermal stress can present a challenge to homeostasis, especially for the cardiovascular system and glycemia. Cardiovascular adjustments are crucial for temperature regulation during heat and cold exposure such that blood must be redistributed toward the periphery (i.e., vasodilation) and toward the core (i.e., vasoconstriction) respectively to maintain a stable core temperature and therefore heat balance. However, vulnerable individuals with a potentially compromised cardiovascular capacity, including many with type 1 and 2 diabetes, may be unable to respond appropriately. Moreover, thermal stress can alter insulin absorption and diffusion properties as well as various counter-regulatory hormones that can greatly impact acute and even chronic glycemia management.

The aim of this review is to characterize the effects of thermal stress (i.e., hot and cold exposure) on individuals with type 1 and 2 diabetes, the consequences for cardiovascular responses and glycemic control, and how fitness and individual characteristics may mediate these effects.

Basic temperature regulation

The fundamental concept of human thermoregulation is the goal to achieve heat balance, or to cause the rate of heat gained/produced to be equal to the rate of heat lost, as depicted in Figure 1. According to the heat balance equation, the rate of body heat storage is determined by the summation of metabolic heat production, dry heat exchange (i.e., radiant, conductive, and convective heat exchange) and evaporative heat loss.[25] While resting metabolic heat production is usually stable (assuming no food is consumed and exposure to cool ambient temperatures is avoided), pronounced increases occur during physical activity or shivering which are dictated by the mass and intensity of contraction of the active muscle groups. On the other hand, dry heat exchange is primarily influenced by changes in central and peripheral blood flow associated with adjustments in blood vessel diameter, whereas evaporative heat loss is determined by the amount of sweat expelled by the activated eccrine sweat glands onto the skin. During thermal stress, sensory information is sent from the peripheral (in the skin and muscle) and central (in the brain) thermoreceptors to the pre-optic anterior hypothalamus of the brain which is believed to coordinate thermoeffector responses to achieve heat balance.[26,27] During heat stress, the hypothalamus signals the dilation of peripheral blood vessels (i.e., to the skin) and an increase in sweat production in order to adjust dry and evaporative heat exchange to prevent large increases in body heat storage, and therefore core temperature (Fig. 1). In contrast, cold exposure is associated with hypothalamic signals to constrict the peripheral blood vessels, minimize sweat production, and increase metabolic heat production (i.e., shivering and non-shivering thermogenesis) during prolonged and/or severe cold exposure to prevent dangerous drops in core temperature.
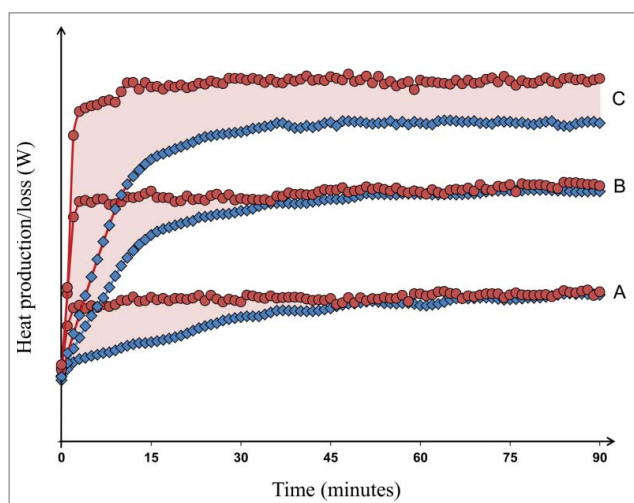
Figure 1. A schematic diagram demonstrating the rate of heat production (red circles, metabolic rate minus rate of external work) and rate of net loss (blue diamonds, dry + evaporative) during prolonged exercise in the heat. The amount of heat stored in the body - represented by the red shaded area - is the cumulative difference between the rates of heat production and whole-body heat loss by combined evaporative (from sweat and respiration) and dry (conduction/convection and radiation) heat exchange. The metabolic heat production during exercise results in elevated body heat storage and a corresponding increase in core and muscle tissue temperatures, the magnitude of which is determined by the relative intensity of the exercise performed. As long as the rate of heat gain does not exceed the body's physiological capacity to dissipate heat, heat balance will be achieved such as during low (A) and moderate intensity exercise (B). However, as exercise intensity (and therefore the rate of heat production) increases a concomitant increase in rate of heat loss is required to offset this higher rate of heat production and achieve heat balance (such as occurs during transition from A to B). However, there occurs a threshold past which the rate of metabolic heat production exceeds the body's physiological ability to dissipate heat (C). As a consequence, the body will continue to store heat for the duration of the exercise period. Noteworthy, exercise that is performed in the heat will present an added heat load for the body and consequently even moderate intensity exercise performed in the heat may become uncompensable (shift from B to C).

Heat stress

The human body retains tight thermoregulatory control about a set temperature of ~37°C,[27] with life-threatening complications arising with core temperature increases as small as 3°C. Various factors including hot and/or humid environmental conditions and physical activity can pose a threat to the maintenance of core temperature. Following afferent input from the central and peripheral thermal receptors, the hypothalamus initiates an increase in heat loss via increases in skin blood flow (i.e., vasodilation) and sweating, both of which are modulated by sympathetic nerves.[28,29] The action of vasodilation opens the skin's blood vessels to allow greater blood flow to the skin which increases skin temperature, and thereby increasing the gradient for dry heat exchange between the skin and the external environment. Sweating, which is known as the primary avenue for heat loss especially during physically activity in the heat, is stimulated by cholinergic nerves to expel sweat onto the skin which is subsequently evaporated.[30] It is the evaporation of sweat that cools the body and as such sweat loss due to dripping provides no thermoregulatory benefit and facilitates a state of progressive dehydration.

One of the strongest determinants of the rate of heat loss is the level of hyperthermia as measured by mean body temperature which has traditionally been defined as a composite of core and skin temperatures.[31] Upon exposure to heat stress (i.e., entering into hot ambient conditions and/or beginning physical activity), there is a progressive increase in mean body temperature. This increase is the result of a lag in the activation of heat loss responses of skin blood flow and sweating which occurs irrespective of the rate of heat gain (as defined by the net environmental and/or exercise-induced metabolic heat load(s) illustrated in Fig. 1).[27] In fact, heat loss is only activated once mean body temperature has surpassed a given onset threshold (see Figure 2A and D). The heat loss responses then increase proportionally to the increase in mean body temperature, the linear portion of which represents the thermosensitivity (see Figure 2B and E). Once the heat loss responses reach maximal values, no further increase in heat loss occurs despite further increases mean body temperature (see Figure 2C and F).

The onset threshold, thermosensitivity and maximal capacity of the heat loss responses for skin vasodilation (Fig. 3) and sweating (Fig. 4) can substantially impact the amount of heat stored. Factors such as aging and diabetes can delay or increase the onset threshold (Fig. 2D) and reduce the thermosensitivity (Fig. 2E) as well as the maximal capacity of the heat loss responses (Fig. 2F) which can allow for greater increases in mean body temperature during heat stress. The evaluation of these parameters can itself provide valuable insight into understanding whether the changes in thermoregulatory function associated with diabetes are mediated via central (e.g., at the controller level of the brain) and/or peripheral [e.g., end-organ (sweat glands, skin vessels)
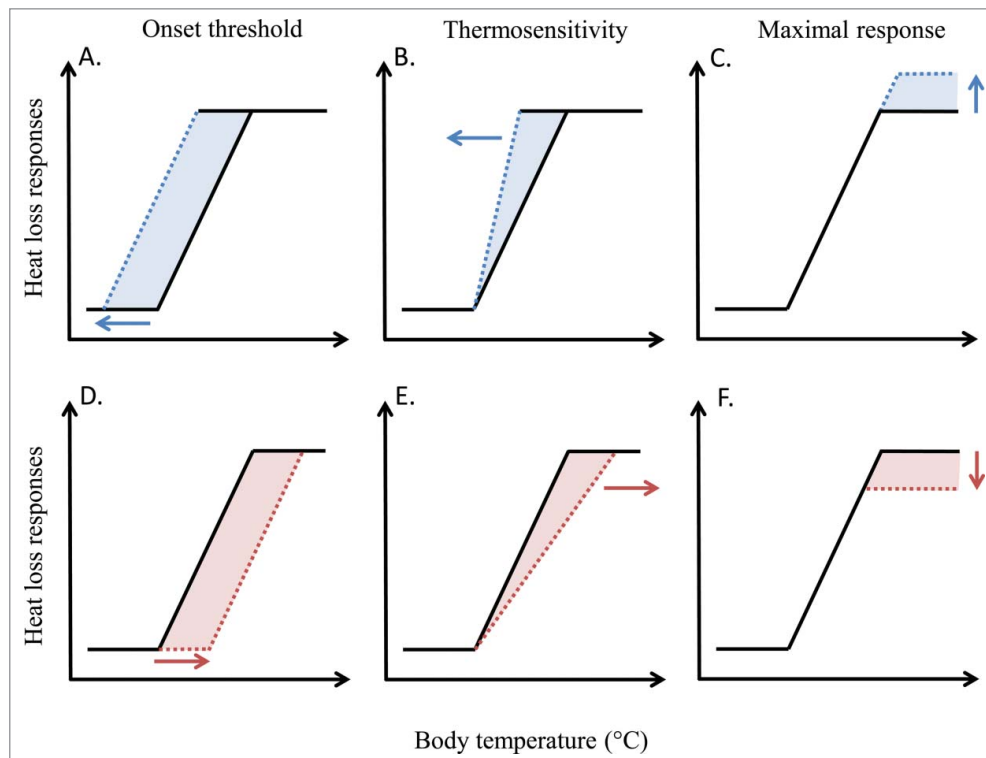
Figure 2. The measurement of the onset threshold, the thermosensitivity, and the maximal or plateau level of local and whole-body heat loss during exposure to heat stress (i.e., with environmental and/or metabolic heat loads). The heat loss response (i.e., skin blood flow and sweating) are activated at a given onset mean body temperature threshold (A and D). The heat loss responses then increase proportionally to the increase in mean body temperature, the linear portion of which represents the thermosensitivity of the response (B and E). Once the heat loss responses reach maximal values, a plateau is observed, whereby no further increase in heat loss occurs despite increasing mean body temperature (C and F). There are number of factors (hydration, acclimation, sex, age, chronic health conditions such as diabetes and others) that can affect the activation of heat loss responses which can result in a decrease (Panels A-C, blue shaded area) or increase (Panels D-F, red shaded area) in the amount of heat stored during heat stress. In the latter situation (i.e., greater heat storage) this can occur when: 1) the onset threshold is shifted to the right, such that a greater change in mean body temperature is required to initiate the activation of the heat loss response (D), 2) the thermosensitivity of the response is decreased, such that a lower change in heat loss occurs for a given change in mean body temperature (E), and; 3) the maximal heat loss response is reduced, such that lower maximal values are attained for a given change in mean body temperature (F).

function]) mechanisms.[32,33] In the context of whole-body heat loss under heat stress conditions which are compensable (i.e., the requirement for heat loss is less than the maximal heat loss), the rate of heat loss will continue to increase until heat balance is achieved wherein the rate heat loss matches the rate of heat gain (see Fig. 1A and B). However, under uncompensable heat stress conditions (i.e., the requirement for heat loss > maximal heat loss), mean body temperature will continue to increase as the rate of heat gain exceeds the body's physiological capacity to dissipate heat as evidenced by the observation of the thermoeffector responses, and therefore rate of whole-body heat loss, reaching their maximum capacity (see Fig. 1C). If left unchecked, the continuous increase in mean body temperature can lead to heat-related illness and/or injury.

Cold stress

Cold exposure can impose a marked physiological stress on humans. To avert cold-induced injuries or death, behavioral strategies (e.g., finding shelter, adding clothing layers, making fire) must be employed in order to prevent precipitous decreases in core temperature.[34] In addition, multiple physiological processes are activated during cold exposure in order to minimize heat loss and under conditions of severe and/or prolonged cold stress, increases in metabolic heat production are observed. Minimizing heat loss is achieved through peripheral vasoconstriction whereas increases in heat production can be elicited by shivering and non-shivering thermogenesis.[35] Increased heat production via shivering employs the skeletal muscles,
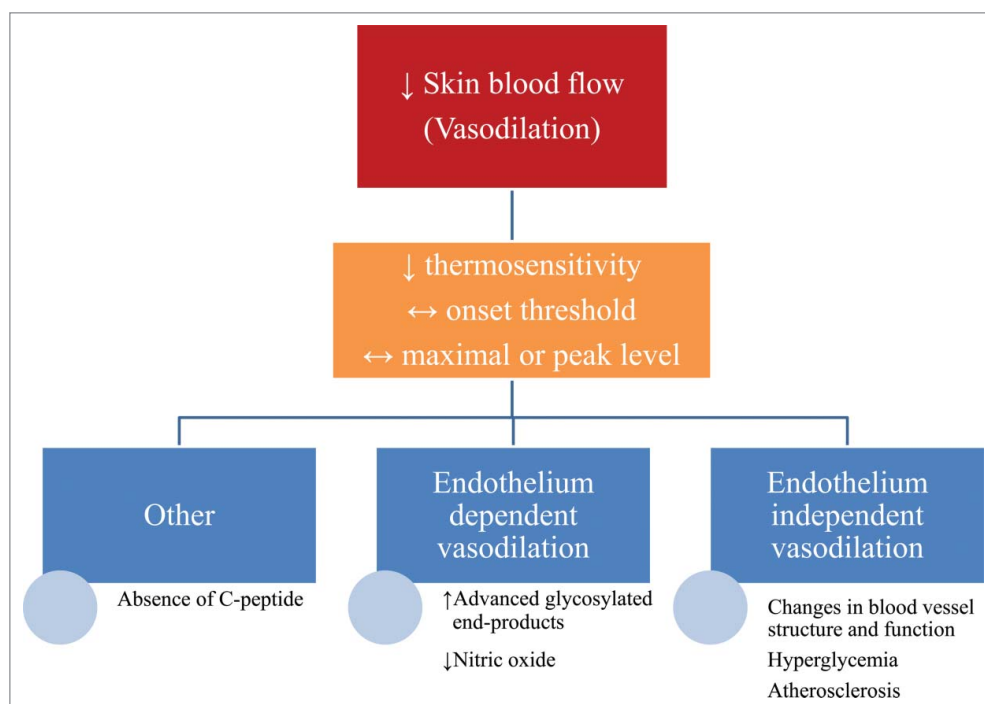
Figure 3. Type 1 and Type 2 Diabetes Mellitus are associated with impairments in vasodilation which explain in part the reduction in the capacity to dissipate heat. This is primarily related to a reduction in the thermosensitivity of the response as the onset threshold and the maximal or plateau level of skin blood flow is similar during heat stress. While the mechanisms remain to be fully elucidated, some studies have found a role for endothelium-dependent and –independent vasodilation as well as other factors (e.g., an absence of C-peptide).

which can represent ~30 kg of a lean 72 kg individual. Skeletal muscle has the greatest capacity of any body tissue to increase the rate of metabolism, and therefore heat production. Shivering intensity is dictated by changes in mean body temperature,[36,37] and maximal heat production of a shivering individual can increase up to 5-fold from baseline or to ~40% of maximal aerobic capacity.[36] On the other hand, non-shivering thermogenesis is primarily mediated by metabolically active brown adipose tissue.[38] Although shivering is undoubtedly the major contributor to increases in heat production, studies postulate that non-shivering thermogenesis remains an important physiological response especially during mild cold exposure.[35]

Type 1 diabetes

Despite the similarities in the nature of complications with type 1 and 2 diabetes, the patient population with type 1 diabetes is generally distinctly different. Individuals with type 1 diabetes are typically diagnosed during childhood or early adulthood (incidence peaks between ages 10-14 years[39]), are leaner and typically have minimal or no comorbidities at diagnosis.[17]

In addition, improved diabetes management and care strategies have led to markedly increased life expectancy along with reduced incidence of associated complications.[40,41] However, longer life expectancy has also caused a rapidly increasing number of older adults living with type 1 diabetes. Diabetes care plans must consider adjustments for the age-related changes in functional status and incorporate appropriate accommodations for individuals who may be less able to manage their glycemia.[42] Furthermore, the early-onset of type 1 diabetes results in a longer burden of disease, and therefore increased diabetes-related complications in the aging population[40] along with lower quality of life in adults with worse glycemic control.[43] Taken together, type 1 diabetes afflicts an increasingly widespread group of patients from the young and otherwise healthy to the older adults with multiple comorbidities.

Heat stress

Most of the studies regarding heat exposure and type 1 diabetes have focused upon local measurements of heat loss and/or thermal sensation to characterize the
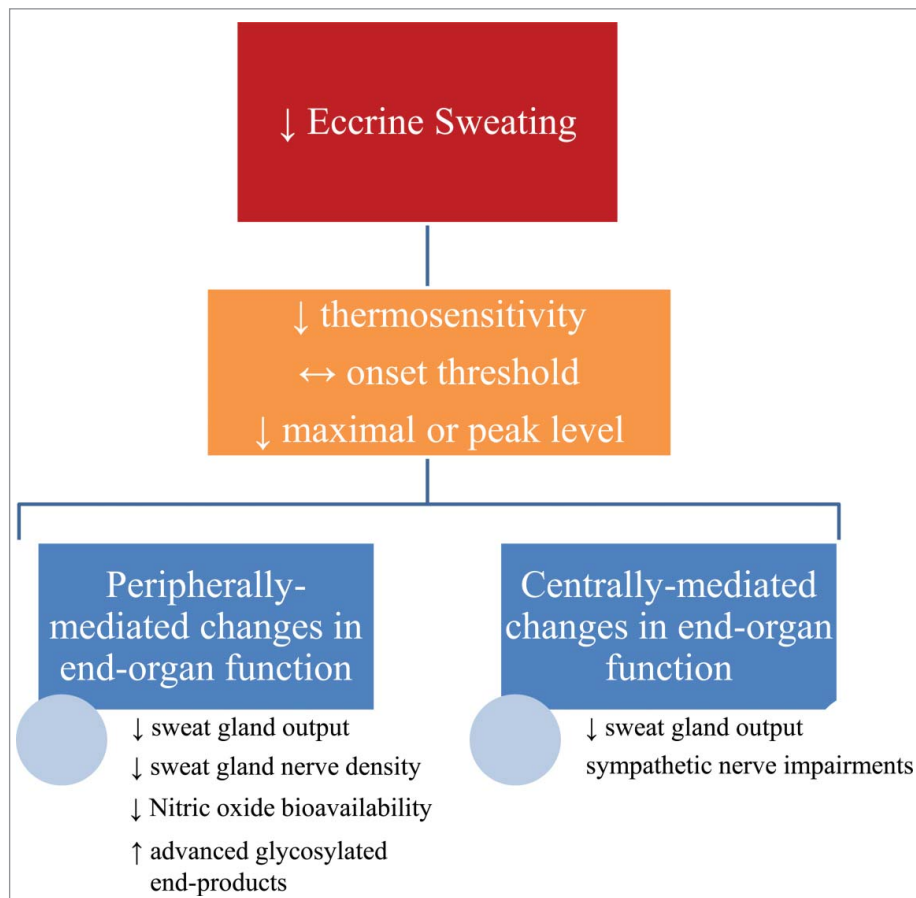
Figure 4. Type 1 and Type 2 Diabetes Mellitus are associated with impairments in eccrine sweating which leads to a marked reduction in the capacity to dissipate heat. This is primarily explained by a reduced thermosensivity and a lower maximal or plateau level of sweating with no changes in the onset threshold. The mechanisms have yet to be completely understood; however, there is evidence for both centrally- and peripherally-mediated changes in the functioning of the sweat glands.

presence and/or severity of neuropathy. In a thermo-comfortable environment (~23-25°C) under resting conditions, individuals with type 1 diabetes have been reported to have greater skin and limb blood flow relative to healthy controls which is thought to be related to moderate vasodilation induced by a general hyper-insulinemic state.[44] However, other findings indicate that maximal cutaneous vasodilation elicited pharmacologically and/or via local heating can be reduced in individuals with type 1 diabetes.[45] On the other hand, it remains uncertain whether the impaired maximal cutaneous vasodilation is paralleled by reduced sub-maximal skin blood flow responses. For instance, a study by Arora et al.[46] reported similar increases in skin blood flow between non-neuropathic individuals with type 1 diabetes and their healthy counterparts (albeit responses were blunted in neuropathic individuals) whereas other work has shown clear diabetes-related impairments in skin blood flow.[47,48] In the context of eccrine sweating, the general pattern in individuals with type 1 diabetes is relative lower body anhidrosis along with upper body eu- or hyperhidrosis[49,50] which can lead to global anhidrosis.[51] Importantly, these reductions in skin blood flow and sweating in those with type 1 diabetes have been related to longer disease duration,[47,52] poorer glycemic control as assessed by higher hemoglobin A1$_c$ (HbA1$_c$) levels,[45,50-52] greater degrees of neuropathy, and/or lower aerobic fitness.[53] Despite the fact that these studies were primarily directed at assessing vasomotor and/or sudomotor function as indices of the extent of diabetes-related complications (e.g., neuropathy), they can provide valuable insight regarding core temperature regulation.

To date, very few studies have examined the effect of whole-body heat exposure under resting conditions with none reporting changes in core temperature.[54-56] In addition, the first study of thermoregulatory control

in young physically active adults (i.e., engaged in physical activity ≥3 times per week for ≥20 min) with type 1 diabetes during dynamic exercise was only published in 2013.[57] Specifically, Stapleton et al.[57] employed a 60-min moderate intensity exercise bout (~400 W or ~40% of maximal aerobic capacity) which was followed by a 60-min of recovery in warm ambient conditions (35°C and 20% relative humidity). In comparing whole-body heat loss via direct calorimetry (a gold standard method for making precise measurements of heat loss by the human body) between individuals with type 1 diabetes and their healthy controls, their findings suggested no differences in heat loss with similar core and skin temperatures, and therefore no diabetes-related impairments in thermoregulation. However, a follow-up study by Carter et al.[58] revealed that while there were no differences in the body's physiological capacity to dissipate heat at moderate rates of heat gain during exercise (i.e., ~400 W) as assessed by the local measurements of skin blood flow and sweating, differences were observed at higher levels of heat stress. Specifically, physically active individuals with type 1 diabetes showed impairments in heat loss at a metabolic heat load >400 W (i.e., 500 and 600 W or ~55 and 65% of maximal aerobic capacity in this study), demonstrating for the first time a heat load-dependent impairment for type 1 diabetes. This diabetes-related impairment in the capacity to dissipate heat was further supported by greater increases in rectal temperature (by ~0.5°C at end-exercise) paralleled by lower thermosensitivity for local skin blood flow and sweating, albeit some regional heterogeneity in the pattern of response was observed. Noteworthy, the impaired thermosensitivity of local heat loss in those with type 1 diabetes led to a lower level of sweating which suggests a lower maximal capacity for heat loss even though the plateau level of skin blood flow was similar between groups.[58] Therefore, even otherwise healthy physically active individuals with type 1 diabetes can have pronounced impairments in core temperature regulation which become apparent at heat loads > 400 W which may be achieved through light-to-moderate cycling or light jogging (see Fig. 5 for a summary of the observations from refs 58 and 59). However, it should be noted that these studies have only examined physically active individuals with relatively well-controlled diabetes (i.e., HbA1$_c$ <8.5% and no clinically diagnosed complications) and that the responses are expected to be further blunted in

those with poor glycemic management, advanced age, and/or neuropathy (Fig. 6).

Studies show that skin blood flow and sweating are rapidly suppressed in the early stages of postexercise recovery (i.e., ~20 min) in healthy individuals despite sustained elevations in core and muscle temperatures. This phenomenon has been explained primarily by a role for nonthermal factors (i.e., baroreceptors, osmoreceptors, metaboreceptors, and mechanoreceptors) which are known to modulate heat loss independent of core temperature (for a recent extensive review, readers are referred to Kenny and Jay[27]). Interestingly, Stapleton et al.[57] reported that while both groups showed rapid decreases in whole-body heat loss following 60 min of exercise, a marginally greater absolute rate of evaporative heat loss was observed in the group with type 1 diabetes by ~25 W relative to the controls. However, this was explained by a slightly greater rate of heat gain associated with an elevated rate of metabolic heat production during the postexercise period along with increased dry heat gain in the group with type 1 diabetes. As a consequence, a comparable reduction in body heat storage and therefore core temperature was observed between groups at end of recovery. In contrast, the study by Carter et al.[58] reported increased hyperthermia in those with type 1 diabetes at the end of higher intensity exercise. In a separate report from the same study (i.e., the same participants) examining the postexercise response in thermal (and cardiovascular responses), McGinn et al.[59] showed that despite these differences in core temperature that persisted throughout the 60 min recovery period, local heat loss responses were similar between individuals with type 1 diabetes and their healthy controls (note: metabolic heat production was not measured during recovery; see Fig. 5). Taken together, it is possible that there are differences in the contribution of the non-thermal factors (i.e., those associated with the activation of sensory end organs [e.g., baroreceptors, metaboreceptors, osmoreceptors, etc.]) which are known to modulate postexercise heat loss in individuals with type 1 diabetes;[27] however, further research is warranted to delineate this possibility.

To date, the mechanisms underpinning the diabetes-related impairments in heat loss responses and core temperature regulation remain largely unresolved. However, some insight related to the diabetes-mediated alterations in skin blood flow may be
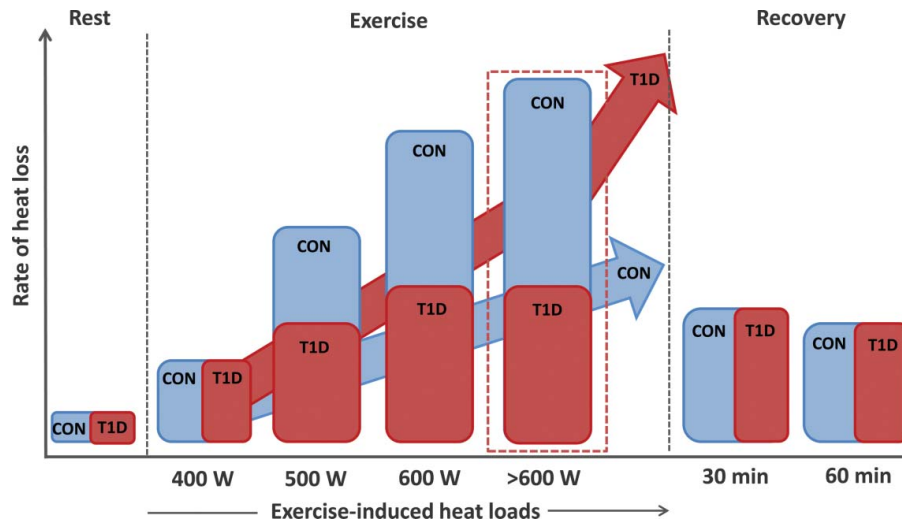
Figure 5. Schematic depicting the change in the rate of heat loss (bars) and the increase in core temperature (arrows) during exercise in those with type 1 diabetes (T1D) and their healthy controls (CON). Studies show that active individuals with type 1 diabetes with good-to-moderate glycemic control (HbA1$_c$< 8.5%) demonstrate a similar capacity to dissipate heat at heat loads ≤ 400 W as compared to their healthy counterparts matched for age, fitness and body composition (see ref 57 and 58). However, diabetes-related impairments in heat loss are observed at progressively greater heat loads leading to significantly greater increases in core temperature (see ref 58). Despite a higher state of hyperthermia measured at end exercise, individuals with Type 1 diabetes demonstrate a similar rate of heat loss relative to their healthy counterparts during the recovery period with core temperature remaining elevated above baseline resting for a minimum of 60 minutes (see ref 59). Future studies are required to determine the extent to which type 1 diabetes reduces the body's maximal ability to dissipate heat such that no further increase in heat loss will occur despite increases in the rate of heat produced/gained (as defined by the dashed contoured bar at a heat load >600W).
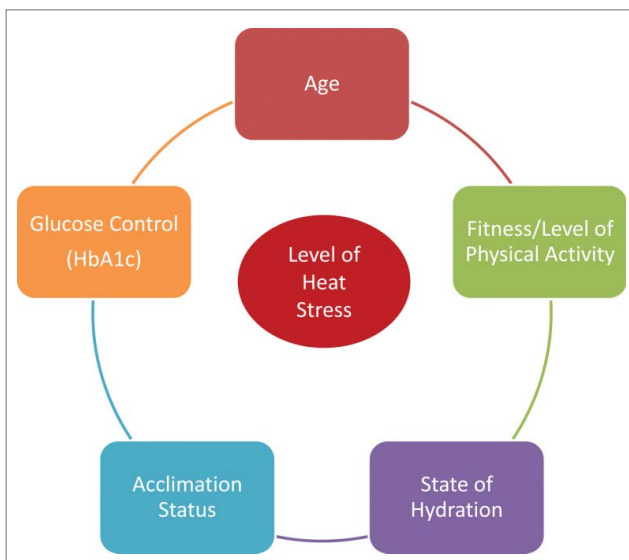

Figure 6. The factors of age, fitness level, hydration status and acclimation status as well as hemoglobin A$_1$c (HbA$_{1c}$) in individuals with diabetes which are well known to impact the capacity to dissipate heat in humans during heat stress associated with a passive heat exposure (e.g., hot ambient conditions), exercise, or a combination of both. While there is a substantial amount of research examining such factors in healthy young adults, there is little known with regards to individuals with Type 1 or Type 2 Diabetes Mellitus.

gleaned from the few studies that have studied skin vascular response and are depicted in Figure 3. For example, the absence of C-peptide (produced in pancreatic islet β cells) is known to have an important role in microvascular blood flow in a manner which is nitric oxide-dependent.[60] In fact, infusion of C-peptide in those with type 1 diabetes was successful in reversing the group's impairment in skin blood flow relative to healthy individuals.[61] Others have noted impairments in endothelium-dependent and endothelium–independent vasodilation[47,48, 62] along with reduced nitric oxide bioavailability due primarily to diminished nitric oxide synthase activity.[63]. In addition, type 1 diabetes has been shown to induce morphological changes in blood vessel structure and function which have a detrimental effect on skin blood flow by lowering the capacity to adjust blood flow in the skin,[64,65] although such changes appear to be strongly associated with glycemic control. In particular, HbA1$_c$ levels >8.5% (indicating chronically elevated blood glucose levels) are strongly associated with reductions in skin blood flow,[66,67] and one study has linked even acute hyperglycemic episodes to irreversible vascular changes which could impair heat loss.[68] Finally, type 1 diabetes is associated with

increased formation of advanced glycosylated end products[69] which can suppress nitric oxide bioavailability and augment basal oxidative stress which affects skin blood flow control.[70,71]

The diabetes-related impairments in sweating are relatively less understood and are illustrated in Figure 4. Lower body anhidrosis is thought to be explained by diabetic neuropathy that is known to begin distally with the nerves of the feet being the most susceptible due to their length. The reasons for existence of early upper body hyperhidrosis remain unclear. While this may be a compensatory response to lower body anhidrosis, it is thought that diabetic polyneuropathy can present in the early stages with increases in sweating to the affected areas,[54,72] and therefore the upper body hyperhidrosis may indicate the early stages of neuropathy. The recent study by Carter et al.[58] reported markedly lower sweating in habitually active individuals with relatively well-controlled type 1 diabetes compared to their healthy counterparts. Such impairments in sweating can lead to pronounced increases in body heat storage and consequently elevated states of hyperthermia. Although they observed similar impairments in sweating at 3 local sites (i.e., on the forearm, chest and upper back), the mechanisms underlying the regional sweating impairments appeared to differ. While sweat rate at the chest was lower as a result of reduced number of heat-activated sweat glands, the reduced forearm sweat rate was attributed to lower sweat output per gland. Given the reduced thermosensitivity of the sweating response in those with type 1 diabetes, Carter et al.[58] surmised that the diabetes-related changes in sweating were due to peripherally-mediated changes such as reduced acetylcholine sensitivity, altered physical properties of the actual sweat glands and/or interruptions in the thermoeffector neural pathways. In fact, the latter mechanism has received some support by observations depicting lower sweat gland nerve densities associated with sympathetic nerve impairments.[73]

Cardiovascular responses

Cardiovascular function under resting conditions in those with type 1 diabetes that are otherwise healthy is generally reported to be similar to their healthy counterparts including cardiac output, heart rate, stroke volume, and blood pressure.[59,74] Individuals with type 1 diabetes are known to be at increased risk for cardiovascular disease and hypertension;[13] however, this can be minimized by healthy habits including physical activity and good glycemic control.[75] On the other hand, baroreflex sensitivity has been reportedly reduced with type 1 diabetes in resting conditions even in otherwise healthy individuals.[76-78] Although it is commonly regarded as a measure of autonomic nervous system function, baroreflex sensitivity is a vital cardiovascular reflex with important implications for blood pressure and possibly thermoregulatory control.[27,79] Furthermore, type 1 diabetes has been closely associated with reductions in blood volume which reduces the total amount of fluid available for circulation.[74,80] Therefore, while any impairments in resting cardiovascular function are minimal or non-detectable, individuals with type 1 diabetes may be at increased risk for cardiovascular-related limitations under stress such as during exercise, especially when performed in the heat due to the exponential increase in the requirements for blood flow to the active muscles.[81]

Exercise is often prescribed as a key component to diabetes management;[82] however, as noted above there may exist cardiovascular impairments with type 1 diabetes. Among these diabetes-related changes include reduced maximum heart rate and stroke volume at submaximal and peak exercise intensity due to diastolic ventricular dysfunction which together decrease cardiac output.[83-85] In addition, a recent study observed that even after accounting for any differences in cardiac function, otherwise healthy individuals with type 1 diabetes had reduced peak blood flow to the active muscles.[74] On the other hand, only one study has examined cardiovascular responses during the postexercise recovery period.[59] There were no statistical differences in cardiac output, stroke volume, or heart rate between the group with type 1 diabetes and the healthy controls; however , McGinn et al.[59] reported a lower magnitude of postexercise hypotension for individuals with type 1 diabetes as early as 20 minutes after exercise which is consistent with prior observations of reduced postexercise muscle blood flow reported in individuals with diabetes.[86] Interestingly, in the study by McGinn et al.[59] the group with type 1 diabetes also had an exacerbated reduction in baroreflex sensitivity during the recovery period. While these cardiovascular impairments

may also have implications for thermoregulatory control in type 1 diabetes, information is lacking regarding the interplay between these 2 systems.

Cold stress

In comparison to heat stress, there is a lack of information regarding the impact of type 1 diabetes on the responses to cold exposure. Based on the observations that individuals with type 1 diabetes demonstrate greater skin blood flow under baseline resting conditions which enhances dry heat loss (this is thought to be associated with the hyperinsulinemic state[44]) combined with the evidence of hypoglycemia-mediated blunting of shivering thermogenesis[87] and reduced thermal sensation,[88] it could be argued that individuals with type 1 diabetes may be at greater risk of a cold-related injury during cold stress.[21] Along these lines, individuals with type 1 diabetes are reported to exhibit reduced cutaneous vasoconstrictor response to a cold-pressor test[45] and to have impaired sympathetic vasoconstriction during application of lower body negative pressure to induce hypovolemic stress.[89] Specifically, the latter was evidenced by reduced redistribution of peripheral blood toward the central circulation and is consistent in males and females.[89,90] Furthermore, type 1 diabetes has been associated with reduced cutaneous vasoconstriction in the post-prandial period, indicating reduced blood flow redistribution to the gut.[91] However, there have also been some conflicting reports with respect to vasoconstrictor activity such that Zomer et al.[92] observed greater urotensin II in the skin resulting in a net vasoconstrictor effect, and vasoconstrictor activity in the dorsal hand veins appears to be enhanced in type 1 diabetes complicated by microalbuminuria.[93] Ultimately, the limited evidence may suggest that individuals with type 1 diabetes may be at greater risk during cold exposure due to impaired peripheral vasoconstriction and redistribution of blood flow; however, no study has directly examined this hypothesis.

Type 2 diabetes

Type 2 diabetes tends to present later in life with a mean onset age of 54 years,[94] although the mean age at diagnosis is rapidly decreasing[95] due in part to the longstanding increase in diagnosis in the pediatric population.[96] In general, type 2 diabetes is linked to general health status and lifestyle as it has commonly been associated with multiple comorbidities including obesity, dyslipidemia, metabolic syndrome, hypertension and other cardiovascular diseases as well as the changes associated with normal aging. Moreover, individuals with type 2 diabetes tend to develop diabetes-related complications at or early after diagnosis including neuropathy and nephropathy along with other micro- and macrovascular impairments. This may be related to the delay in treatment of type 2 diabetes as a result of individuals going undiagnosed for many years. In fact, it is currently estimated that over 8 million cases of type 2 diabetes are undiagnosed in the United States alone.[11] Similar to type 1 diabetes, the complications associated with type 2 diabetes are typically associated with the level of glycemic control (i.e., $HbA1_c$); however, it has been suggested that the presence/severity of neuropathy is more closely explained by an inverse relationship with high-density lipoprotein-cholesterol.[97] Collectively, individuals with type 2 diabetes are a particularly vulnerable population group due to their tendency to have relatively poor overall health combined with multiple comorbidities.

Heat stress

Most of the current research regarding the thermoregulatory capacity of individuals with type 2 diabetes considers the responses in the context of defining the severity of neuropathy along with other diabetes-related complications. As such, many have only evaluated the local heat loss responses of the hands and feet. In this regard, it has generally been reported that individuals with type 2 diabetes have impaired skin blood flow responses evoked by pharmacological stimuli,[98,99] local skin heating,[100,101] and whole-body heating (see Fig. 3).[100,102] Importantly, these effects appear to depend on fitness such that those with type 2 diabetes who engage in physical activity have reduced impairments in skin vasodilation, albeit individuals with type 2 diabetes exhibit reduced maximal skin blood flow irrespective of fitness.[103] On the other hand, studies of local sweating in type 2 diabetes have generally found that these individuals have impaired sweating responses compared to their healthy counterparts,[54,100,104] despite one study reporting otherwise.[105] The changes in regional sweating with type 2 diabetes are comparable to those which are observed for type 1 diabetes such that there is relative lower

body anhidrosis with euhydrosis or hyperhidrosis on the upper body.[54] While these studies have implications for whole-body temperature regulation during heat stress, the evidence regarding the impact of heat stress (as induced by hot environments, physical activity, or both) on individuals with type 2 diabetes remains limited.

Epidemiological data during heat waves and extreme heat events support the notion that type 2 diabetes is associated with a markedly greater risk for heat-related illness and/or death.[19] In fact, individuals with type 2 diabetes have up to a 56% greater risk for hospitalization and/or mortality during a heat wave.[106] One recent study assessed the influence of age and type 2 diabetes during passive heat exposure in a room set at 43°C for 3 hours.[107] While the study supported a robust suppression in whole-body heat loss in older adults, individuals with type 2 diabetes did not demonstrate any greater impairment in heat dissipation compared to their age-matched controls (Fig. 7). In contrast, Kenny et al.[108] recently reported that relatively active individuals with type 2 diabetes have pronounced reductions in the capacity to dissipate heat during a 60 min exercise bout (~370 W of metabolic heat production or ~60% of maximal aerobic capacity) as assessed by whole-body direct calorimetry (Fig. 7). During the exercise bout, the group with type 2 diabetes stored ~1.54-fold more heat than their healthy counterparts which was associated with lower evaporative heat loss. Despite this greater amount of heat that was accumulated during the exercise, the diabetes-related impairment in heat loss persisted into the 60 min recovery such that the healthy controls lost ~2-fold more heat relative to the group with type 2 diabetes due to a slight, but persistent, difference in the rate of dry heat exchange (although this was not statistically significant).[108] Noteworthy, both studies (i.e., during passive and exercise-induced heat exposure)[107,108] included individuals with type 2 diabetes who were otherwise generally healthy (i.e., good glycemic control and no diabetes-related complications). Considering the possibility for augmented/additive effects to the impairments in heat loss that are associated with neuropathy, cardiovascular diseases, lower fitness and/or morbid obesity, further investigation is warranted to evaluate the level of risk that would be experienced by these individuals.

To date, there have been few studies examining the mechanisms underlying the type 2 diabetes-related impairments in heat dissipation; however, some information may be gleaned from those studies aimed primarily at assessing the presence of neuropathies (see Figs. 3 and 4). The reduction in nitric oxide bioavailability in individuals with type 2 diabetes is well established[98,99,109] and may be further exacerbated by the presence of atherosclerotic plaques which is known to adversely alter endothelial function through interfering with nitric oxide signaling.[110] In fact, one study reported that the relative nitric oxide-dependent vasodilation during whole-body passive heating was similar between healthy controls and those with type 2 diabetes; however, absolute skin blood flow was lower in the latter group.[109] Moreover, there is evidence to support an endothelium-independent component to the impairment in vasodilation as observed during exogenous administration of a nitric oxide donor (i.e., sodium nitroprusside).[99] Of particular importance, these diabetes-related changes in skin blood flow appear to be closely associated with the duration of diabetes and/or the presence of related complications.[98,99] While little information is available regarding the central versus peripheral mechanisms underlying diabetes-related skin blood flow responses, one study implicated a lower onset threshold for vasodilation as the primary factor to explain a lower skin blood flow; an indication that the modulation of skin blood flow is mediated via central mechanisms.[102]

The mechanisms responsible for the diabetes-related impairments in sweating during heat stress remain incompletely understood and as noted earlier, most of the information is provided from studies not aimed to examine thermoregulatory control. As in the case of individuals with type 1 diabetes, regional differences in the sweating response are also apparent in individuals with type 2 diabetes. For example, Petrofsky et al. 2005[100] showed that while sweating on the arms and legs tends to be reduced during isometric handgrip exercise to exhaustion, forehead sweat rate was actually elevated relative to the controls. The primary factors associated with this decrease in sweating include longstanding diabetes, poor glycemic control, and the presence of neuropathy which seem to have an important role in altering the peripheral properties of the sweat glands.[54,111] For instance, the sweat glands from individuals with type 2 diabetes with poor glycemic control exhibit exacerbated reductions in peri-glandular nerve terminals and in the innervation index.[111,112] On the other
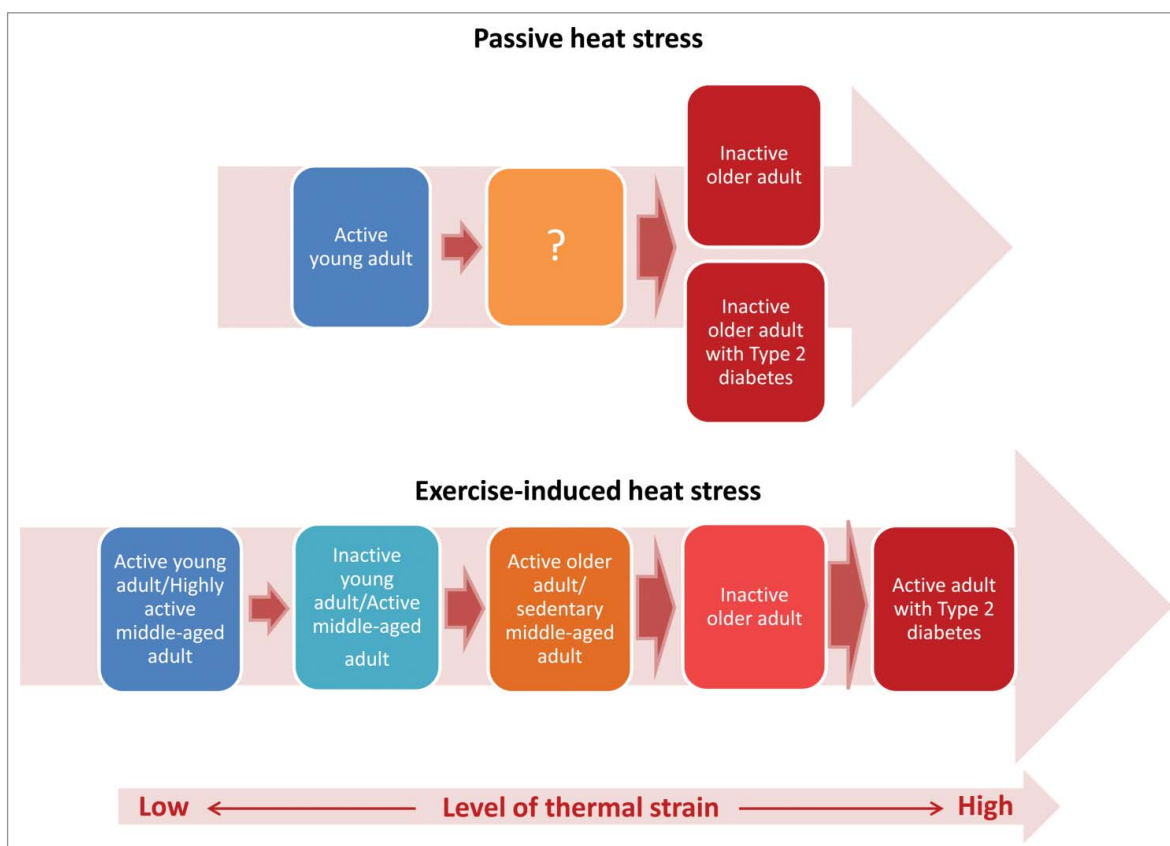
Figure 7. Schematic depicting the predicted level of thermal strain, and therefore the amount of heat stored, for a given level of heat stress induced by a passive exposure (top panel) or exercise (bottom panel). During a passive heat exposure, young adults store less heat than their inactive older counterparts. However, recent evidence shows no difference in the level of heat storage between older adults and their counterparts with Type 2 diabetes (see ref. 118). It remains unclear how factors such as level of physical activity/fitness, acclimation, hydration status, blood glucose control (for individuals with diabetes) may influence this pattern of response (orange square). In contrast, the age-related decrement in heat loss during exercise is further exacerbated in older adults with Type 2 Diabetes and the level of fitness appears to be an important component (see ref. 119).

hand, the impairments in sweating during heat stress may be related to the reduction in nitric oxide bio-availability given that the role for nitric oxide-induced sweating during exercise has been recently well established.[113,114]

Cardiovascular responses

Due to the fact that most individuals with type 2 diabetes are older adults, the impact of type 2 diabetes alone can be confounded by the typical age-related impairments in cardiovascular function. A recent report indicated that individuals with type 2 diabetes at rest had higher heart rate (presented as a percentage of maximum) along with reduced stroke volume and cardiac output compared to healthy young controls, but did not differ from their age-matched (i.e., older) controls.[107] On the other hand, other studies have reported that while the decline in cardiovascular function with aging is similar to those with type 2 diabetes, their absolute level of function is lower[115] such that aging and type 2 diabetes have synergistic negative effects. In line with this, individuals with type 2 diabetes show impairments relative to age-matched controls in heart rate variability (an indicator of autonomic nervous system function) at rest and during postural manipulation.[116] In fact, some evidence indicates that heart rate variability can be a predictor for any diabetes-related complications.[117] Importantly, these effects are strongly dependent upon glycemic control, albeit it has been postulated that episodes of acute hyperglycemia exert more damage than chronically poor management of glycemia.[118]

It is well established that individuals with type 2 diabetes have reduced exercise capacity relative to their healthy counterparts. Although the mechanism(s) underlying this functional impairment is not clear, it is thought to be associated with a dampened increase in

cardiac output during exercise due to left ventricular diastolic dysfunction.[119,120] Moreover, a recent study has noted a ~20% reduction in exercise capacity in their participants with uncomplicated type 2 diabetes relative to their healthy counterparts. This was linked to a marked decrease in cerebral perfusion during exercise as a consequence of lower cardiac output.[121] Importantly, individuals with type 2 diabetes may also have difficulties adjusting blood flow during bouts of exercise given that the evidence to suggest pronounced impairments in vasodilator capacity in this group (Fig. 3).[122] With respect to cardiovascular control during heat stress, it is alarming to note the lack of information presently available. For instance, type 2 diabetes is associated with reduced sympathetic neural control of blood pressure[123] which manifests as greater orthostatic intolerance compared to age-matched controls.[124] In addition, individuals with type 2 diabetes exhibit a decline in baroreflex sensitivity[125] which is closely associated with the level of insulin resistance.[126] Consequently, it would be expected that individuals with type 2 diabetes are less able to maintain blood pressure and cardiovascular stability during an episode of extreme heat exposure and/or exercise. In contrast, a recent study of a group with type 2 diabetes demonstrated that the changes in cardiovascular measures (i.e., cardiac output, stroke volume, heart rate, total peripheral resistance, blood pressure, and limb blood flow) during a 3-hour passive exposure to extreme heat (43°C) did not differ relative to their age-matched healthy counterparts.[107]

Other comorbidities

It cannot be ignored that type 2 diabetes is often accompanied by one or more other health conditions (obesity, hypertension, cardiovascular disease) which can further affect an individual's ability to dissipate heat during a heat stress. Several studies have examined the ramifications of heat stress in obese individuals and those with chronic health conditions such as hypertension, cardiovascular disease and others.[127-142] In these individuals, heat stress can worsen already limited physical activity levels and increase the feeling of discomfort by aggravating disease-specific symptoms.

Changes in body composition occur with age such that older adults tend to have greater body fat and less muscle mass with this pattern of response being more pronounced in individuals with type 2 diabetes.[132,142] While these changes are multifactorial (e.g., changes in hormone signaling, metabolic activity, dietary intake, and/or level of physical activity), they can have an important impact on the body's physiological capacity to dissipate heat. It is generally thought that obesity is a contributing factor to the elevated states of hyperthermia observed during exercise. This is supported by the observation that young overweight and obese (body mass index > 27) physically active adults are 3.5 times more likely to experience a heat-related fatality compared to lean age-matched individuals.[129] While there are a limited number of studies examining the effects of heat stress in older obese individuals during exercise, it has been shown that obesity is associated with reductions in heat tolerance and impairments in the activation of heat loss responses of skin blood flow and sweating.[134,141] This is exacerbated by reductions in whole-body heat exchange associated with the smaller body surface area-to-mass ratio in obese individuals.[143] Specifically, an obese person has a smaller body surface area-to-body mass ratio for effective sweat evaporation than a leaner person of the same height since his/her greater body mass is not proportional to a difference in surface area of skin to interface for heat exchange with the environment. Further, the specific heat capacity of adipose tissue is less than that of fat-free mass. Thus, for individuals with a higher body-fat mass, a given amount of heat storage per unit body mass will cause a greater increase in core temperature. To date it remains unclear to what extent the presence of type 2 diabetes in obese individuals may lead to greater impairments in heat dissipation and thereby increasing the risk of heat-related injuries. However, one study examined whole-body heat dissipation during exercise in the heat in older overweight (% body fat) adults with (35%) and without (33%) type 2 diabetes.[108] The older adults with type 2 diabetes stored 1.5-times more heat than their non-diabetic counterparts which was attributed to diabetes-related impairments in heat loss. While it is not possible to discern if the effect of obesity *per se* on heat dissipation may be aggravated in individuals with type 2 diabetes, excess in-patient admission rates suggest otherwise. In fact, studies show that individuals with type 2 diabetes have a comparable relative risk to that of a non-diabetic obese individual for a hospital admission induced by a heat-related ailment (33 vs. 20% respectively).[139]

Epidemiological studies demonstrate an increase in morbidity and mortality in individuals with

hypertension.[139] During heat stress, especially during exercise in the heat, hypertensive individuals experience greater elevations in blood pressure due to increased peripheral resistance which can restrict heat loss due to the reductions skin blood flow, which ultimately lead to more pronounced increases in core temperature. This response has been attributed in part to changes in microvasculature structure (thickened media, increased in smooth muscle layers, etc.). However, the effects on skin blood flow have yielded mixed results when assessed under passive heating conditions[128,131,136] whereas consistent reductions in skin blood flow have been measured during exercise in the heat.[137,138] To the best of our knowledge, the effects on sweating have not been studied although medication use (e.g., diuretics) could have profound effects on heat dissipation during heat stress. In fact, some studies suggest that the use of antihypertensive medications (diuretics, vasodilators, β-blockers) can reduce heat tolerance during exercise in the heat.[144,145]

In individuals with cardiovascular disease, heat stress is associated with a reduction in exercise capacity and an increase in disease-related symptoms, making them more vulnerable for morbidity. Healthy older adults have an altered cardiovascular response to heat stress compared to their younger counterparts. Minson et al.[140] showed that older men have a markedly lower increase in total blood flow directed to the skin during a passive heat stress maintained to the individual's limit of thermal tolerance. In the case of the younger males, the increase in skin blood flow was the result of both an increase in cardiac output and a redistribution of splanchnic and renal circulations, whereas in the older males, both cardiac output and blood redistribution from splanchnic and renal circulations were profoundly reduced. These age-related changes in cardiovascular function to heat stress is further impaired in individuals with pre-existing cardiac dysfunction[127] such that increases in skin blood flow and therefore heat exchange is severely compromised.[130,133] Heart failure and peripheral arterial disease are the most common initial manifestations of cardiovascular disease in type 2 diabetes[146] and adults with diabetes have heart disease death rates 2- to 4-fold greater than their non-diabetic counterparts. Whether or not this is paralleled by a greater risk of a heat-induced mortality and morbidity is unclear. Dehydration associated with prolonged exposure to extreme heat conditions can induce significant alterations of blood composition (increased in red blood cell count, blood viscosity and platelet counts) which, if left unchecked, can increase the risk of coagulation, and subsequently cerebral and coronary thromboses.[135] The risk is especially greater in individuals with type 2 diabetes who may experience greater levels of dehydration due to hyperglycemia and/or medication use. Ultimately, any factor compromising normal cardiovascular function and therefore skin blood flow will augment the risk of heat-related injury.

Cold stress

Prior evidence indicating that hyperinsulinemia, which is known to be present in individuals with type 2 diabetes due to reduced insulin sensitivity, can be associated with moderate skin vasodilation in resting conditions.[44] However, individuals with type 2 diabetes appear to have lower skin blood flow relative to their age-matched controls.[18] Although this may be perceived as beneficial in the context of minimizing heat dissipation during cold exposure, type 2 diabetes is also associated with marked impairments in vascular responsiveness to cold. This was best evidenced by Stansberry and colleagues[45] who showed reductions in the contribution of local, reflex, and centrally-mediated mechanisms which can determine skin blood flow. Furthermore, this blunted responsiveness is at least in part attributed to the reduction in the control of blood vessel diameter by the sympathetic nervous system.[45,123] Collectively, there is some evidence to indicate that individuals with type 2 diabetes may be less able to prevent decreases in core temperature associated with cold exposure; however, more information may be gleaned from studies in healthier older adults. In fact, previous work has postulated that diabetes is akin to a state of advanced aging (i.e., diabetes tends to accelerate any age-related changes).[45,147] Along these lines, older adults are known to have a reduced ability to defend core temperature during cold exposure, even that which is relatively mild.[148,149] This has been associated with numerous factors including blunted sympathetic outflow to the skin,[150] reduced production/release of vasoconstrictor neurotransmitters[151,152] and changes in thermoafferent signaling;[153] however, it remains unclear how these factors may apply to individuals with type 2 diabetes.

Most of the research regarding the effects of cold exposure in type 2 diabetes is associated with its therapeutic potential. One of the physiological defenses for preventing a decrease in core temperature during cold exposure is a greater rate of metabolic heat production induced by shivering and non-shivering thermogenesis.[35] Along with increasing whole-body energy expenditure, mild cold exposure activates brown adipose tissue which is highly metabolically active and oxidizes triglycerides and glucose as fuel.[154] The activity of brown adipose tissue has been shown to be characterized by uncoupling protein-1, a mitochondrial protein, and has been reported to have a pronounced role in whole-body thermogenesis even under resting conditions.[155] While brown adipose tissue activity is reported to be relatively lower in individuals with type 2 diabetes relative to their age-matched controls, its activity may be increased with cold acclimation. Specifically, Blondin and colleagues[156] showed that with cold acclimation (i.e., 2 hours of exposure to 10°C for 20 days over 4 weeks) brown adipose tissue volume and oxidative capacity were markedly increased in healthy individuals. Furthermore, cold acclimation can alter insulin sensitivity which is one of the key aspects in type 2 diabetes. In fact, Hanssen et al.[157] reported that only 10 days of cold acclimation (14-15°C) in individuals with type 2 diabetes induced a 43% increase in insulin sensitivity which was explained by a 60% increase in GLUT-4 translocation (i.e., the membrane channel that allows glucose to enter a muscle cell or adipocyte). Surprisingly, these improvements in insulin sensitivity surpass even those of long-term exercise training which is currently regarded as the best management strategy for type 2 diabetes.[158] Taken together, it appears that mild cold exposure may be useful for the management of type 2 diabetes as a third lifestyle factor (along with diet and exercise) to optimize health.[24,159] However, further examination is required to determine the long-term effects of cold exposure and the optimal exposure level that is both realistic and effective. Moreover, it remains unclear as to how diabetic neuropathy would impact activation of brown adipose tissue in individuals with poor glycemic management and if this is related to brown adipose tissue mass.

Glycemic control during thermal stress

It is well established that glycemia levels decrease in those with diabetes during an acute exercise bout, with more pronounced reductions observed during aerobic activities.[160] Hot ambient conditions can also independently modulate glycemia by increasing insulin absorption and are reported to have additive effects to exercise in decreasing blood glucose levels.[56] These findings were supported during exercise wherein 75% of participants with type 1 diabetes required glucose supplementation during 90 min of cycling[58] as well as in type 2 diabetes by Hooper[161] who noted that a 3 week exposure in a hot tub (6 times per week for 30 minutes in 38-41°C water) resulted in a rapid decrease of $HbA1_c$ by ~1% and fasting blood glucose by ~1.3 mmol·L^{-1} (both of which are clinical relevant improvements). Even local heating of the insulin injection site can lower post-prandial glycemia through increasing insulin absorption and activity,[162,163] and has been suggested as a potential avenue to improve long-term glycemic control.[162] The mechanisms for these improvements remain unclear; however, it has been postulated that increases in muscle blood flow associated with heating[164] and/or activation of heat shock protein 70.[165]

Consistent with these findings during heat stress, seasonal variations in glycemia have been reported such that $HbA1_c$ levels for type 1 diabetes are clinically lower during the spring/summer relative to the autumn/winter months[166,167] with differences recently noted to be as high as 3%.[168] Moreover, Tsujimoto et al.[168] reported that in line with the seasonal changes in $HbA1_c$, severe hypoglycemic episodes are almost twice as frequent in the summer months in Tokyo, Japan (reported average low temperature in the fall/winter of 6.9°C and high temperature in the spring/summer of 25.9°C). While these differences may be related the concomitant seasonal changes in physical activity, a recent meta-analysis indicated that the long-term effects of physical activity on $HbA1_c$ are inconclusive.[169] In contrast, the differences in glycemia in a colder environment may be related to counter-regulatory hormone signaling such as increases in plasma cortisol production together with greater glucocorticoid responsiveness which results in lower insulin sensitivity.[170] While no studies have yet assessed the direct impact of acute or chronic glycemia management on thermoregulatory responses to cold exposure, one study has indicated that short-term changes in $HbA1_c$ levels are closely and inversely correlated with the cardiovascular response to a cold pressor test.[171]

Despite these clinically relevant seasonal variations in the control of blood glucose levels for type 1 diabetes, a growing body of evidence indicates that

individuals with type 2 diabetes are less susceptible to such environmental factors. Interestingly, cold exposure is suggested to improve glycemic control for type 2 diabetes through improvements in insulin sensitivity as described above. Moreover, Tsujimoto and colleagues[168] reported that individuals with type 2 diabetes had a similar frequency of severe hypoglycemic episodes throughout the year and no significant seasonal differences in HbA1c. This occurred despite the fact that individuals with type 2 diabetes tend to take fewer steps per day (i.e., an indicator of the level of physical activity) during the autumn/winter compared to the spring/summer months.[172] The mechanism underlying these divergent responses in glycemia between those with type 1 and type 2 diabetes in response to environmental factors is unknown and deserves further scrutiny. However, it is important to note that glycemic control is highly dependent upon the individuals, their level of adherence to the treatment program, and many other personal factors that remain to be fully understood.

From a thermoregulatory perspective, hypoglycemia is known to induce sympathetic activation as evidenced by marked increases in sweating, limb blood flow, heart rate, and blood pressure.[173] While this may result in a decrease in core temperature during resting conditions, the associated dysfunction of the autonomic nervous system may eliminate any potential benefits during whole-body heat stress.[59,76] Similarly, episodes of hyperglycemia can also have an important negative impact on core temperature regulation. Specifically, hyperglycemia can lead to increases in plasma osmolality which has been independently associated with impairments in sweating and skin blood flow.[174] Furthermore, hyperglycemia can induce dehydration through osmotic diuresis[175] which can lead to hypovolemia without adequate fluid replacement. Recently, a few studies demonstrated that the combination of hyperosmolality and hypovolemia presented augmented effects to further exacerbate the impairments of heat loss in healthy individuals.[27,174] In contrast, a different study demonstrated that an acute episode of hyperglycemia (as induced by hyperinsulinemic-hyperglycemic clamp) did not impair nitric oxide-mediated skin microvascular function,[176] albeit impairments of other vasodilator mechanisms were not evaluated. Finally, no study to our knowledge that has assessed the impact of acute hyperglycemia respect to thermoregulatory sweating.

Effects of physical fitness

The effects of aerobic fitness along with short- and long-term exercise training have been widely studied in the context of glucoregulation in type 1 and 2 diabetes. Despite this, a recent meta-analysis of the randomized trials of aerobic or resistance exercise on glycemic control in individuals with type 1 diabetes by Yardley et al.[169] concluded that there is insufficient evidence to ascertain the effect of exercise training on HbA1c. In fact, while a positive effect of exercise training has been shown in type 1 diabetes,[177] others have found no effect[178,179] and even a negative effect[180] on HbA1c. On the other hand, the effects of exercise training on glycemic control with type 2 diabetes is much better established. A recent meta-analysis by Umpierre et al.[181] reported a mean decrease in HbA1c following a structured exercise intervention >12 weeks of ~0.7%. The analysis also revealed that structured exercise training of at least 150 minutes per week yielded superior results of a ~0.9% reduction in HbA1c[181] which have also been associated with fewer diabetes-related complications.[182] Noteworthy is that greater benefits occurred in individuals with type 1 and type 2 diabetes with worse glycemic control prior to the exercise intervention.[169,182]

Aerobic fitness is an important determinant of health status for any individual and higher aerobic fitness is associated with lower all-cause mortality.[183] In the context of thermoregulatory control, higher levels of aerobic fitness and or physically activity have been suggested to improve the capacity to dissipate heat during exercise which may be explained by regular endurance exercise inducing partial acclimation (Figs. 6 and 7).[184,185] However, some have reported no differences in heat loss following short-term exercise training[186] or between independent groups with large differences in aerobic fitness in young individuals.[187] A recent study by Stapleton and colleagues[188] showed that the age-related decline in aerobic fitness (~7% per decade[189]) explained some of the age-related impairments in heat dissipation during exercise. Moreover, a group of middle-aged fit males matched for age (~48 years) and physical characteristics with a group of middle-aged unfit males exhibited greater whole-body heat loss by up to 44% during exercise (Fig. 7).[188] Altogether, aerobic fitness in healthy adults likely plays an important role in the capacity for heat loss and explains some of the attenuated heat

dissipation in older adults, albeit the mechanisms remain poorly understood. With respect to individuals with diabetes, none of the exercise studies have considered fitness as a potential factor as the healthy controls were all matched for maximal aerobic capacity along with age and physical characteristics.[57-59,108] Therefore, the role of aerobic fitness remains unclear regarding thermoregulatory control along with autonomic nervous system function and cardiovascular responses in individuals with type 1 and type 2 diabetes, especially during exercise-induced heat stress.

Diabetes and the older worker

One of the developing areas relating to the prevalence and consequences of type 2 diabetes is the aging workforce. Advanced age is a particularly important risk factor for type 2 diabetes, with diabetes prevalence rate reaching as high as 33% in older adults who are obese.[190] Given that the mean age of the workforce is increasing rapidly, employers are faced increasingly with the challenge of accommodating individuals with chronic health conditions such as type 2 diabetes. Importantly, a diagnosis of any chronic health condition has a negative impact on the productivity of the worker almost immediately with a noticeable reduction in work output within 1 year.[191] To date, there have been few studies in the area of chronic health conditions and the older worker; however, based on the available evidence it would be expected that individuals with type 2 diabetes would exhibit decreased work output and a reduced capacity to perform occupational tasks particularly in physically demanding jobs and especially in hot environments. For example, individuals with type 2 diabetes are documented to have a lower maximum aerobic capacity[119,120] relative to their age-matched controls. In addition, their increased susceptibility to heat stress indicates that individuals with type 2 diabetes may be at greater risk for heat-related illness during work activities performed in the heat (e.g., mining, electrical utilities work).[108] Indeed, it has been previously reported by Lavigne et al.[192] that individuals with type 2 diabetes have reduced productivity which is incremental based on the disease duration, although the presence of type 2 diabetes was not a factor associated with absenteeism. Importantly, it was noted in this study that the productivity losses were not reflected in a higher productivity cost since individuals with type 2 diabetes had lower salaries on average.[192] Thus, the area of type 2 diabetes in the older worker is becoming an important area of focus with the development of exposure limits along with specific guidelines and recommendations needed as a priority in order to ensure the protection and safety of these individuals.

Future directions

Despite the fact that the incidences of type 1 and type 2 diabetes are increasing worldwide, there is an alarmingly small amount of research regarding its impact on the responses to thermal stress and the implications for the cardiovascular system and glycemic control. Furthermore, there remain no studies to our knowledge on thermoregulation or the control of sweating and/or skin blood flow that address a less common form of diabetes called latent autoimmune diabetes in adults. It is unclear how this form of diabetes would differ from type 1 and type 2 diabetes mellitus and this warrants investigation. Figure 8 depicts an overview of the current knowledge regarding the effects of diabetes during the exposure to heat and cold along with the cardiovascular implications and the potential role for fitness and glycemic control. Despite the fact that exercise is recommended as a cornerstone for optimal diabetes management and that individuals with diabetes are more vulnerable during heat stress, very few studies have directly examined the thermoregulatory responses of type 1 diabetes (Fig. 5)[57-59] and only one study has considered the impact of type 2 diabetes on the body's physiological capacity to dissipate heat (Fig. 7).[108] Future research must be aimed to define exposure limits for these individuals and to determine the effects of critical factors such as the extent to which individuals with type 1 and 2 diabetes have an impaired capacity to dissipate heat during and following passive and/or exercise-induced heat stress, the impact of hydration status and hyperglycemia on the ability to regulate core temperature, and the effects of maintaining or increasing aerobic fitness all in the context of autonomic nervous system function, cardiovascular strain and blood glucose control (Figs. 6 and 8). In addition, special consideration in the future should be given to research in thermoregulation in older adults with longstanding diabetes and those diagnosed with diabetes-related complications including neuropathy. Similar to heat stress, there is a paucity of studies examining the
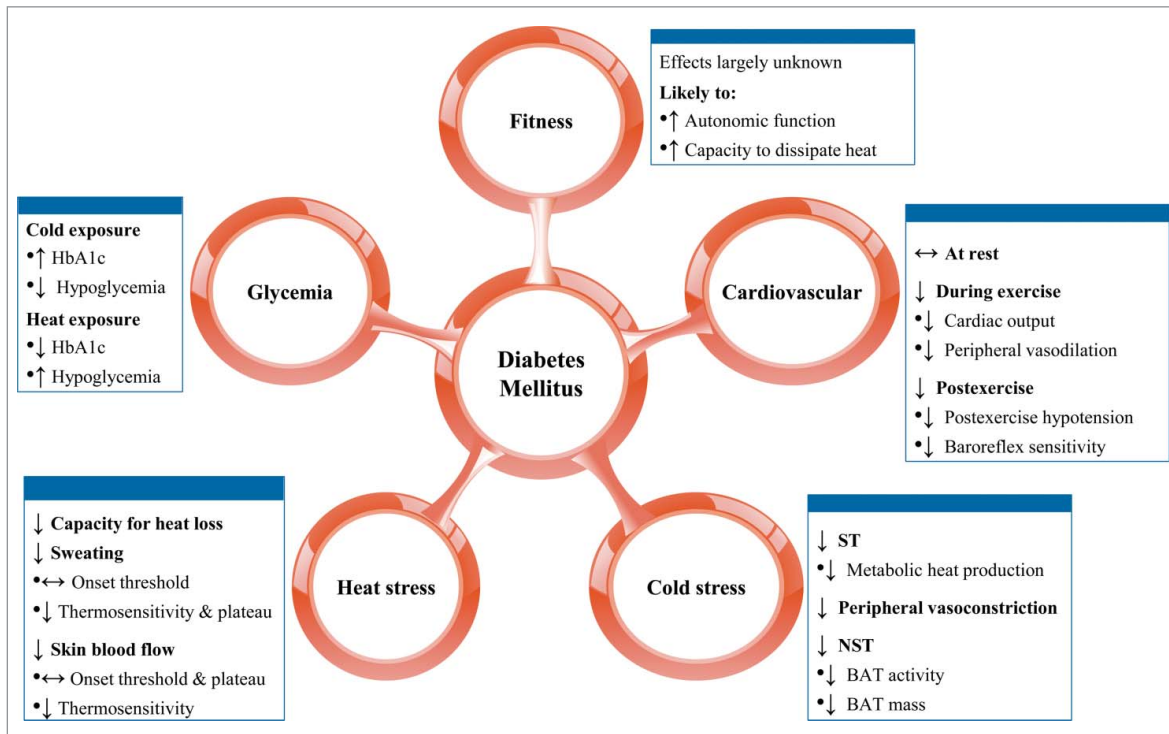
Figure 8. This represents a summary of the consequences of diabetes mellitus with respect to glycemic control, fitness, and cardiovascular function as well as during exposure to cold and heat stress. Each of these concepts is discussed in detail in this review. While the most commonly tracked and reported diabetes-related complications include neuropathy, retinopathy, and nephropathy, individuals with diabetes can be at particular risk during exposure to heat and cold stress. More research is required to further characterize these disturbances in temperature regulation and cardiovascular control as well as the potential role for fitness and glycemic control. HbA1$_c$, hemoglobin A1$_c$; ST, shivering thermogenesis; NST, non-shivering thermogenesis; BAT, brown adipose tissue.

effects of cold stress on individuals with diabetes. Although mild cold stress may have therapeutic potential for individuals with type 2 diabetes, further research is warranted to more clearly delineate the conditions under which benefits occur and to identify the pathways and proteins that may be specifically targeted for treatment. In addition, more research should focus on the potential for individuals with diabetes to be at greater risk for injuries during cold exposure given their reduced capacity for vasoconstriction and altered sympathetic control of the blood vessels.

Conclusions

Type 1 and 2 diabetes mellitus are both associated with reduced ability to maintain core temperature during thermal stress. This has been related to impairments in the body's ability to dissipate heat mediated via increases in skin blood flow and sweating during heat stress as well as an attenuated capacity to increase metabolic heat production and to decrease skin blood flow during cold stress. To date, minimal research has

been conducted with the aim of evaluating thermoregulatory control during thermal stress in individuals with diabetes. The available evidence depicts a group that is vulnerable to cold- and heat-induced injuries/illnesses; however, it is important to note that these impairments may be mitigated at least in part by maintaining good glycemic control, maintaining or increasing aerobic fitness, and preventing diabetes-related complications. While some information may be gleaned with regards to the impact on cardiovascular and blood glucose control due to the relative inability to adequately regulate core temperature, more research is necessary to define the underlying mechanisms for these responses and the short- and long-term consequences on the overall health of individuals with diabetes.

Abbreviations

$HbA1_c$ hemoglobin A1$_c$

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