Body Temperature Regulation During Exercise and Hyperthermia in Diabetics

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Chapter 6

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Abstract

Thermoregulatory function, that is, heat dissipative responses such as skin blood flow (SkBF) and sweating to an increased body temperature, is critical during physical work or exercise in warm and hot conditions and during hyperthermia. Thermoregulatory function is associated with individual somatotype, fitness level, normal aging, and physiological status and diseases. Individuals with type 2 diabetes have decreased thermoregulatory responses compared with healthy counterparts, characterized by decreased SkBF and sweating. The decreased SkBF and sweating would be associated with the reduction in nitric oxide bioavailability and endothelial functions in skin vasculatures, also with central mechanisms, and so on. Aerobic exercise training and/or acclimation to the heat improve heat dissipative responses in healthy subjects. The effects of exercise training in type 2 diabetics on glycemic control are well established while it remains unclear that high levels of aerobic fitness or exercise training in diabetics improve thermoregulatory function during heat stress.

Keywords: thermoregulation, sweat rate, skin blood flow, plasma volume, aging, diabetes

1. Introduction

Individuals are more likely to become exhausted and to develop heat-related illnesses when physical work or sporting activities are performed for a prolonged time in warm and hot conditions or direct sunlight compared to in cooler conditions. Thermoregulation is one of the most important physiological functions for when individuals are exposed to extreme hot environments. The incidence of heat-related illnesses is particularly great if physical work or

exercise is performed at higher intensities and in higher ambient temperatures (T_a) and relative humidity (RH) [1]. In addition, the incidence is greater in persons who are dehydrated, who are not acclimated to hot environments, or who have low levels of physical fitness and daily activity even if they are healthy [1]. More importantly, the incidence is greater in individuals with obesity, diabetes mellitus, and cardiovascular diseases, due to impaired thermoregulatory responses [1, 2]. It is also greater in individuals with attenuated thermoregulatory responses, such as those with skin grafts, spinal cord injuries, and multiple sclerosis [3–5]. Moreover, an extreme hot environment can be dangerous for the elderly (even those who are healthy) because of the normal aging process [1, 2]. Over the last two decades, the morbidity and mortality of heat-related illnesses has rapidly increased in Japan because of the rapidly aging population and global warming [6]. This chapter first discusses thermoregulation during work and exercise in warm and hot conditions and the possible physiological effects of humoral and other important factors on thermoregulation. Second, the effects of diseases such as diabetes on thermoregulatory responses are discussed.

2. Thermoregulation in warm and hot conditions

Core body temperature is determined by the heat equilibrium between heat gain and loss [1]. Typically, core body temperature is elevated when we face continuous whole-body work and exercise. This is because only approximately 20% of the energy produced in contracting muscles is used for muscle contraction; the remaining 80% is converted to heat energy, and therefore exercise causes an increase in muscle temperature. The heat is distributed to the body by the circulation and increases body temperatures. Therefore, greater exercise intensities are associated with greater heat production during exercise. However, although core body temperature elevates rapidly within several minutes of starting exercise, heat dissipation mechanisms are activated sufficiently to balance heat production and eventually the increase in core body temperature reaches a steady state. The cutaneous vasculature and sweat glands are thermoregulatory effectors of the skin and promote heat loss by increasing skin blood flow (SkBF) via cutaneous vasodilation and by sweating, respectively [1]. The heat generated in contracting muscles is transferred, because of circulation of blood, to the skin surface; thus, skin surface temperature is elevated by the increased SkBF. The heat transferred to the skin surface is released to the surrounding air according to the thermal gradient between the skin and the air (non-evaporative heat dissipation). Therefore, in a cool environment, non-evaporative heat dissipation is effective; however, in warm environments, when T_a is higher than skin temperatures (~30°C), it becomes ineffective or even negative and acts as a source of heat gain. Conversely, sweating enhances heat loss via sweat evaporation from the skin surface to the air (evaporative heat dissipation). Evaporative heat dissipation is determined according to the gradient of water vapor between the skin surface and the surrounding air. Therefore, it is available regardless of T_a and is the main and critical heat loss mechanism when T_a exceeds ~30°C; however, it is attenuated in a humid environment. Consequently, when heat gain exceeds heat loss during high-intensity work and/or exercise in a hot and humid environment, core body temperature increases rapidly. Therefore, these conditions increase susceptibility to heat-related illnesses.

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Physiologically, SkBF and sweating are regulated by body core and skin temperatures (thermal factors) and also other (non-thermal) factors [1]. Body core temperature is monitored continuously by central thermoreceptors. On the other hand, skin temperatures are monitored continuously by the peripheral thermoreceptors. These receptors send received thermal information through an afferent pathway to the thermoregulatory center in the preoptic/anterior hypothalamus [1]. When the hypothalamic thermoregulatory center determines that core and skin temperatures are elevated compared to the set point, SkBF and sweating are increased through the reflex efferent pathways of sympathetic nerve systems [1]. In humans, SkBF and sweating are neutrally controlled via two distinct skin sympathetic nerves. A sympathetic adrenergic vasoconstrictor system is one of the neural control mechanisms for SkBF and the other is a separate sympathetic cholinergic vasodilator system [1]. Sweating is controlled by sympathetic cholinergic nerves [1]. In addition, non-thermal factors modify the thermal reflex, including central commands, mechano- and metabo-reflexes, arterial and cardiopulmonary baroreflexes, blood volume and osmolality, and mental stimuli [1]. During exercise, they exert different effects on SkBF and sweating responses [1]. Typically, SkBF at the same levels of core and skin temperatures is lower during exercise than resting conditions, and this restriction is greater at higher exercise intensities. Conversely, sweating at the same levels of core and skin temperatures is likely to be higher during exercise than resting conditions.

When levels of dehydration worsen, the risk of heat-related illnesses is much higher during work or exercise in a hot environment [7]. Rothstein and Towbin [8] described for the first time the effects of dehydration on thermoregulation in humans. They reported that an ~0.3°C increase in rectal temperature is caused by every 1% body weight loss by sweating in breaks between exercises when soldiers march in the desert. This is because, as non-thermal factors, dehydration-induced hypovolemia and hyperosmolality limit the response to enhance SkBF and sweating to increased body temperature. Decreased body fluid volume and increased osmolality change dramatically during exercise even in a cool environment. Indeed, plasma volume (PV) is decreased with an increased intensity of exercise. In maximal exercise, the decrease in PV is reached by approximately 300–500 mL (8–15%). Increased capillary fluid filtration from the intravascular to the extravascular spaces due to an increase in blood pressure and peripheral vasodilation during exercise causes the PV change. Additionally, metabolites accumulated in the intracellular fluid of contracting muscles such as lactic acid increases free-water shift from the plasma to the intracellular fluid through the interstitium based on the osmotic gradient [9]. It is estimated to be ~1 L of the volume shifted to the contracting muscles at maximal exercise. About half of this water is from PV [10]. In addition, plasma osmolality (P_{osm}) is increased from ~285 mosmol/kgH_2O at rest to over 300 mosmol/kgH_2O at maximal exercise due to accumulated metabolites. These humoral changes are not caused by dehydration due to sweating; rather, they are associated with the exercise itself. Because they are observed within several minutes after the start of exercise, in addition, when exercise is performed in warm and hot conditions, hypohydration due to the decrease in PV and hyperosmolality due to the increase in P_{osm} during exercise is exacerbated because of increased SkBF and sweating for thermoregulation. Enhanced SkBF induces a reduction in venous return to the heart due to pooling of excessive blood in dilated peripheral vasculature of the skin [11]. Additionally, ~10% of the sweat volume is lost from plasma fluids, and P_{osm} is increased according to sweat rate because sweat is hypotonic compared to body fluids. These humoral changes enhance the load on the circulation and act as limiting factors for thermoregulation.

Nadel et al. [12] first showed that isotonic hypovolemia (change in PV, −700 mL; body weight, −2.7%) achieved by diuretic administration before exercise induced upward shift of the esophageal temperature (T_{es}) threshold for the onset of cutaneous vasodilation by 0.4°C during exercise at 55% of maximal oxygen consumption rate (VO_{2max}) in a hot environment (T_a 35°C). It also reduced the SkBF at peak value by about 50% compared to control condition. Besides, Mack et al. [13] reported that an acute reduction in venous return to the heart induced by application of −40 mmHg lower body negative pressure (LBNP) decreased SkBF and elevated T_{es} during exercise at an intensity corresponding to a heart rate of 125 beats/min in a warm environment (T_a, 28°C). In contrast, all techniques to acutely increase venous return during exercise, including isotonic hypervolemia with saline infusion [11], postural change from upright to supine position [14, 15], head-out water immersion [16], or continuous negative pressure breathing [17], enhanced the response to increase SkBF to an increased core body temperature during exercise. From these observations, the response to increase SkBF to an increased core body temperature during exercise is attenuated by dehydration-induced hypovolemia via the cardiopulmonary baroreflex. Recently, Ogawa et al. [18] reported that the efferent sympathetic signals to skin vasculature, that is, the skin sympathetic nerve activity (SSNA), component synchronized with the cardiac cycle was decreased by postural change from supine to 30° head-up tilt during hyperthermia (T_{es} increased ~0.7°C) with passive heating and that the responses were correlated with the decrease in cutaneous vasodilation. With these data, they suggested that the SSNA component synchronized with the cardiac cycle was likely to contribute to the suppression of cutaneous vasodilatation.

Previous studies have suggested that the response to increase sweat rate during exercise is also attenuated by hypovolemia. Fortney et al. [19] presented that the ability to enhance sweating of the chest and forearm to an increase in T_{es}, but not the T_{es} threshold at the start of sweating during cycle ergometer exercise (65–70% VO_{2max}) in a warm environment (T_a, 30°C; RH, 40%), was attenuated by isotonic hypovolemia (9% reduction in plasma volume induced by diuretics) prior to exercise. Additionally, Mack et al. [13] showed that LBNP at the level of −40 mmHg during exercise dampened the sweat rate and SkBF to increased T_{es}. Dodt et al. [20] also observed decreased skin sympathetic nerve activity following LBNP in passively heated subjects. In contrast, Kamijo et al. [21] reported that isotonic hypovolemia induced by diuretic (−10%) before exercise dampened increases in SkBF, similar to the results of Nadel et al. [12]. However, it did not dampen the increase in sweat rate during exercise at 60% VO_{2max} in a warm environment (T_a, 30°C; RH, 45%). Thus, the effects of hypovolemia on sweat rate are still debatable.

Plasma hyperosmolality suppresses the response to increase SkBF and sweating during exercise. Fortney et al. [22] showed that 10 mosmol/kgH_2O increases in P_{osm} achieved by hypertonic saline infusion before exercise caused an increased T_{es} thresholds for cutaneous vasodilation and sweating by 0.2°C. In addition, the sensitivity to increase SkBF in response to increased T_{es} decreased during exercise at 70% VO_{2max} in a warm environment (T_a, 30°C; RH, 40%). Additionally, onset of SkBF and sweat rate responses to increased core body temperature is delayed by plasma hyperosmolality. Takamata et al. [23] showed a linear upward shift of the T_{es} thresholds with several levels of increase in P_{osm} by hypertonic saline infusion. They suggested with these data that T_{es} thresholds for cutaneous vasodilation and sweating during passive heat stress (lower-leg water immersion, 42°C) at rest

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shifted upward by 0.044°C and 0.034°C per 1 mosmol/kgH_2O increase, respectively. More intriguingly, they also suggested that the upward shift in T_{es} thresholds during exercise were caused by an increased P_{osm} induced by exercise. The increased T_{es} thresholds at a given increase in P_{osm} during exercise were identical to those during resting passive heat stress [23]. Mitono et al. [24] supported this evidence by indicating that when the increase in P_{osm} during exercise was attenuated by hypotonic saline infusion prior to exercise, the delayed onset of cutaneous vasodilation in response to increased T_{es} during exercise was normalized. It has been suggested that the response of the thermoregulatory center was attenuated by plasma hyperosmolality via osmoreceptors.

As described above, dehydration is a limiting factor for heat loss mechanisms during exercise in the heat. These mechanisms prevent cardiovascular failure caused by reduction in venous return to the heart due to blood pooling in dilated peripheral skin vasculature and reductions in PV due to sweating. Indeed, it has been reported that, when drinking such a small amount of water so as not to change PV and P_{osm} in dehydrated individuals, thirst sensation and plasma vasopressin secretion induced by increased P_{osm} are released rapidly by a stimulation of oropharyngeal reflexes [25, 26]. It also simultaneously releases the dehydration-induced attenuated responses of SkBF [21] and SR [26].

3. Effects of exercise training on thermoregulation in warm and hot conditions

Thermoregulatory responses are improved by aerobic and endurance exercise training, resulting in reduced physiological strain and therefore enhanced cardiovascular and exercise capacities during exercise in warm and hot conditions. These adaptations are remarkable when exercise training is performed in the heat [1]. After a 10-day training period in a cool condition (T_a, 20°C), SkBF and sweat rate responses to increased T_{es} during exercise (T_a, 25°C) are enhanced. After a subsequent 10-day training period in a hot condition (T_a, 35°C), these responses improved further [27]. The increased SkBF and sweating responses are characterized by the early start of cutaneous vasodilation and sweating responses to increased T_{es} [28, 29] and the increased sensitivity to increase SkBF and sweat rate in response to an increased T_{es} compared with before exercise training [28, 29]. It is suggested that the mechanisms of the increase in thermoregulatory responses with exercise training are similar to those following acclimations to repeated heat exposures, including adaptations of the thermoregulatory center and thermoregulatory effectors [1, 12] as well as an increase in VO_{2max} [30] and PV [28, 31, 32].

It is suggested that the exercise-induced PV expansion is primarily associated with an increase in total volume of extracellular fluid [33]. An increase in plasma protein (mainly albumin content) also contributes by drawing fluids into the intravascular space from the interstitium [33–35]. Facilitated Na^+ and water reabsorption [33, 36] and an enhancement of voluntary fluid intake with increased thirst sensation [37] (associated with an activated renin-angiotensin-aldosterone system and vasopressin release) during and after exercise or dehydration are suggested as mechanisms of training-induced increases in extracellular fluid volume [38].

Increases in plasma protein may be due to activated hepatic plasma protein synthesis [39, 40] and enhanced translocation of protein to the intravascular space from the interstitium [41] coincide with a restricted transcapillary escape ratio of protein [42].

PV expansion by exercise training results in a reduction in lactic acid concentration in the blood at the same absolute intensity of exercise (an enhanced lactate threshold), which contributes to a suppression of increase in P_{osm} during exercise. This mechanism contributes to the downward shift of the body core temperature threshold for cutaneous vasodilation and sweating after training. Moreover, expanded PV increases venous return to the heart and cardiac filling pressure and therefore enhances cardiac stroke volume. It also improves the responses of SkBF and sweat rate to increased core body temperature during exercise [11, 16, 17]. Indeed, an increase in cardiac stroke volume and also the sensitivity of increase in SkBF to increased T_{es} during exercise in a warm condition (T_a, 30°C) was closely correlated to a PV expansion by a 10-day endurance training (60% VO_{2max} for 1 h/day at 30°C) [28]. Additionally, Goto et al. [43] reported the influences of protein and carbohydrate (CHO) supplementation just after exercise (Pro-CHO; 0.36 g protein/kg and 3.6 kcal) during the 5-day training period (70% VO_{2max} for 30 min/day) in a warm environment (T_a, 30°C) on PV and thermoregulatory responses. They suggested that, in the Pro-CHO group, plasma albumin content (Alb_{cont}) and therefore PV increased by ~10% and ~8%, respectively. These were significantly higher than the increase of ~4% in the placebo intake control group (CNT; 0.9 kcal and 0 g protein/kg body weight). They attributed the increase in Alb_{cont} to activated hepatic albumin synthesis following exercise due to the increased substance bioavailability [39, 40] and also the effects of insulin on protein synthesis in hepatocytes [44]. Most notably, the sensitivity of an increase in SkBF and sweat rate to increased T_{es} enhanced after training more in the Pro-CHO group compared with the CNT group. Additionally, both groups showed a significant decrease in heart rate and T_{es} during exercise after training period. However, these adaptations were more prominent in the Pro-CHO group than in the CNT group, indicating decreased cardiovascular and thermal strains after the training period with PV expansion.

In addition, Ikegawa et al. [31] supported the observations by Goto et al. [43] by presenting an increased PV with an early shift of the onset of the cutaneous vasodilation and sweating responses to an increased T_{es} after the same training protocol. Further, the early shift of the onset of the cutaneous vasodilation and sweating responses was wholly or partly diminished after the expanded PV by training was reduced to the pre-training level by using the diuretics. Furthermore, Ichinose et al. [28] showed that 10 days of exercise training (60% VO_{2max} for 60 min/day at 30°C) attenuated the sensitivity of the upward shift of T_{es} threshold for cutaneous vasodilation with the increased P_{osm} by hypertonic saline infusion, though the threshold for sweating was not changed. Furthermore, they suggested that increased PV after training correlated with the attenuated sensitivity to hyperosmolality in each individual, suggesting that the attenuation is associated with the stretch of cardiopulmonary baroreceptors induced by PV expansion. Thus, the enhanced thermoregulation and cardiovascular capacities after exercise training are closely associated with PV expansion in addition to the neural adaptation of the thermoregulatory center and thermoregulatory effectors [1, 12].

The Na^+ concentration of sweat is important to maintain PV during exercise. It decreases after exercise training or heat acclimation due to an enhanced Na^+ reabsorption at the sweat gland

duct induced by an enhanced sensitivity to aldosterone [45]. To maintain PV during exercise, hypotonic sweat is advantageous because hypotonic sweat loss causes a greater increase in osmolality of extracellular fluid. It promotes the shift of water from intracellular to extracellular fluid space according to the osmotic gradient between the spaces [45]. This therefore attenuates the decreased PV and venous return to the heart. As a result, the decreased thermoregulatory responses with a sweating loss at a given volume are attenuated with low Na^+ concentration in sweat [46]. Moreover, the delayed onset of cutaneous vasodilation and sweating responses to increased T_{es} at a given increase in P_{osm} was attenuated in heat-acclimated individuals in whom an increased P_{osm} by sweating loss at a given volume was enhanced due to low Na^+ concentration in sweat [46].

4. Effects of biological aging on thermoregulation in warm and hot conditions

The susceptibility to heat related-illnesses in the elderly [6] is caused by a deterioration in thermoregulatory responses with aging [47, 48]. Previous studies have indicated that even healthy elderly individuals have an impaired thermal perception [49] and impaired autonomic [50, 51] and behavioral [52, 53] thermoregulatory responses. A recent study indicated that skin warmth detection thresholds in the extremities and the whole-body thermal sensation deteriorated with normal aging under both normothermic conditions and under passive heat-induced mild hyperthermic conditions [54]. Decreased VO_{2max} and cardiovascular capacity associate with the deteriorated thermoregulation with aging [51]. Nevertheless, elderly individuals with a similar level of VO_{2max} to young individuals are known to show an attenuated response of SkBF both during passive heat stress in whole-body or local-body parts and during exercise under a hot environment compared to young individuals [55, 56]. Specifically, Kenney et al. [56] used bretylium tosylate to block the local release of norepinephrine on the forearm skin. They suggested that the attenuated SkBF response to hyperthermia during exercise in a hot condition was caused not by an enhanced vasoconstrictor system but mainly by a decreased sensitivity of the active vasodilator system to increased T_{es}. In addition, the whole-body and local sweat rate in response to passive heat stress or exercise are attenuated in the elderly compared to young adults [57].

Several physiological changes with advancing age, for example, such as decreased PV and increased P_{osm} at baseline [58], diminished thirst sensation [58], and responses in antidiuretic hormone and aldosterone after thermal dehydration [38], are suggested to be associated with the decreased thermoregulatory responses in the elderly. Decreased renal concentrating ability [59] and lower reabsorptive ability of sweat gland ducts [59] with advancing age are also suggested to be associated with the deteriorated thermoregulatory responses with aging. Vasoconstriction of splanchnic organs during exercise, which enhances the redistribution of cardiac output to the skin vasculature, is associated with increased cutaneous vasodilation in youth, which is also attenuated with aging [60]. Furthermore, elderly individuals commonly take a variety of prescription drugs that may affect thermoregulatory responses and body fluid regulation [1]. Exercise training and heat acclimation can improve the blunted body fluid regulation and thermoregulation with aging, although generally the improvement of these is lower or limited relative to their younger counterparts.

5. Effects of type 2 diabetes on thermoregulation in warm and hot conditions

Type 2 diabetes typically presents later in life with a mean onset age of 54 years [61]. Type 2 diabetes is associated with multiple comorbidities, including obesity, dyslipidemia, metabolic syndrome, hypertension, and other markers of cardiovascular diseases in addition to the changes associated with aging. Most of the research examining ability of thermoregulation in type 2 diabetic patients has considered not only to estimate itself but also the responses to evaluate the severity of neuropathy along with other diabetes-related complications. Many studies have only measured the local heat dissipative responses of the hands and feet. It is generally reported that type 2 diabetic patients have attenuated SkBF responses evoked by pharmacological stimuli [62, 63], local skin heating [64, 65], and whole-body heating [64, 66]. Importantly, these effects appear to depend on physical fitness level. Type 2 diabetic engaging in physical activity has reduced impairments in skin vasodilation compared with type 2 diabetics who are not physically active [67]. Conversely, studies of local sweating in type 2 diabetics have generally found that these individuals have impaired sweating responses compared to their healthy counterparts [64, 68, 69], despite one study reporting otherwise [70]. The changes in regional sweating with type 2 diabetes are comparable to those observed with type 1 diabetes, such that there is relatively lower body anhidrosis along with euhydrosis or hyperhidrosis compared to the upper body [68]. While these studies have implications for whole-body temperature regulation during heat stress, the evidence regarding the impact of heat stress (as induced by warm and hot environments, physical activity, or both) on type 2 diabetics remains limited.

Kenny et al. [71] recently reported that relatively active type 2 diabetics who were otherwise generally healthy (good glycemic control and no diabetes-related complications) have significantly decreased whole-body heat loss during exercise for 60 min (~370 W of metabolic heat production or ~60% of the predetermined VO_{2max}) as assessed by whole-body direct calorimetry. During the exercise bout, due to the lower evaporative heat loss in type 2 diabetes, they stored ~1.5-fold more heat than their healthy counterparts. Regardless of the greater amount of heat accumulation during exercise, the diabetes-related impairment in the capacity to dissipate heat persisted into the 60-minute recovery. Healthy groups lost ~twofold more heat relative to the group with type 2 diabetes, which was associated with slightly and no statistically significant, but sustained difference in the rate of non-evaporative heat loss [71].

6. The mechanisms underlying type 2 diabetes-related impairments in heat dissipation

To date, few studies have examined the mechanisms underlying 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. The reduction in nitric oxide bioavailability in individuals with type 2 diabetes is well established [62, 63, 72, 73] and may be further exacerbated by the presence of atherosclerotic plaques which are known to adversely alter endothelial function through interfering with nitric oxide signaling [74]. In fact, one study reported that the relative nitric oxide-dependent vasodilation during whole-body passive

heating was similar between healthy controls and type 2 diabetics; however, absolute SkBF was lower in the latter group [72]. 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 (e.g., sodium nitroprusside) [63]. Importantly, these diabetes-related changes in SkBF appear to be closely associated with the duration of diabetes and/or the presence of related complications [62, 63]. There is little report on the central versus peripheral mechanisms that form the basis of diabetes-related SkBF responses; one study indicated that onset of vasodilation responses to increased core body temperature was delayed and it was the primary factor, explaining lower SkBF in patients with type 2 diabetes mellitus. This indicates that central mechanisms contribute to the modulation of SkBF [66].

The mechanisms responsible for diabetes-related impairments in sweating during heat stress remain incompletely understood and most of the information is provided from studies which have not examined thermoregulatory control. Petrofsky et al. [64] indicated that, during isometric handgrip exercise to exhaustion, sweating on the arms and legs was significantly lower, but only forehead sweat rate was actually higher in type 2 diabetics than the controls. The primary factors associated with this modulation in sweating include long-term diabetes, poorly controlled glycemia, and the presence of neuropathy. Diabetic neuropathy seems to have an important role in altering the sweat gland innervations [68, 75]. Luo et al. [75, 76] showed that the sweat glands in type 2 diabetics with poor glycemic control exhibit exacerbated reductions in periglandular nerve terminals and in the innervation index. Impairments in sweating during heat stress may also be related to the reduction in nitric oxide bioavailability since the role of nitric oxide-induced sweating during exercise has recently been proven [77, 78].

7. Effects of hyperglycemia on thermoregulation during thermal stress

Hyperglycemia can have an important negative impact on body core temperature regulation. Specifically, hyperglycemia can lead to increases in P_{osm} which have been independently associated with impairments in sweating and SkBF as described in the earlier section [79]. Furthermore, hyperglycemia can induce dehydration through osmotic diuresis [80] which can lead to hypovolemia without adequate fluid replacement. Recently, studies have demonstrated that the combination of hyper osmolality and hypovolemia augments any effects to further exacerbate impairments in heat dissipation in healthy individuals [81, 82]. In contrast, acute hyperglycemia (induced by hyperinsulinemic-hyperglycemic clamp) did not result in the impairment of NO-mediated skin microvascular function [83].

8. Effects of exercise training on thermoregulation in the elderly individuals

Several longitudinal studies have reported that heat dissipative responses during exercise in a hot environment are enhanced when aerobic training is performed under hot or even cool to thermoneutral conditions by initially sedentary elderly individuals [30, 60, 84] and young individuals [27–29]. Thomas et al. [30] reported that a 16-week aerobic training program increased

VO_{2max} by ≥5% and advanced onset of cutaneous vasodilation in response to an increased mean body temperature during exercise in a hot environment (T_a, 36°C) both in young and in elderly individuals. They also suggested that an enhanced sensitivity of the active vasodilator system contributes to the enhanced cutaneous vasodilation [30]. Additionally, Okazaki et al. [84] supported and extended these results by showing that onset of cutaneous vasodilation and sweating responses to an increased T_{es} during exercise in a warm environment (T_a, 30°C) were advanced after an 18-week aerobic and resistance training under cool to thermoneutral conditions in initially sedentary elderly individuals. The improvements in VO_{2max} were 20 and 10%, respectively, in each study. However, both studies indicated that the sensitivity of increase in SkBF and sweat rate to an increased mean body temperature or T_{es} did not increase after training. Further, Okazaki et al. [84] indicated that a diminished increase in PV following training period in elderly individuals was associated with the unchanged sensitivity, by showing a linear correlation between changes in the sensitivities and those in PV following the training period. Similarly, in young individuals, the increase in PV is considered to be the major mechanism which contributed to the improvement of thermoregulatory responses by exercise training as described in the earlier section. This results from increased venous return to the heart by increasing cardiac stroke volume and/or by suppressing baroreflex-induced reduction of skin vasodilation [11]. Additionally, Ho et al. [60] showed that splanchnic and renal vasoconstriction during exercise were increased in young individuals but not in elderly individuals following aerobic training period. Thus, in elderly people, exercise training improved VO_{2max} but generally diminished the enhancement of thermoregulation compared with younger counterparts [60, 84].

The primary limiting factor for the blunted increase in PV with aerobic training in elderly people is an attenuated increase in Alb_{cont} with exercise [35, 84, 85]. Other factors are likely to be a reduced fluid intake after thermal dehydration [38, 58] or water deprivation [86] with aging. Accordingly, enhanced albumin synthesis in the liver in response to exercise is one mechanism of the increased Alb_{cont} after aerobic training in the young individuals [39, 40]. In regard to this point, the response to increase Alb_{cont} after aerobic training is smaller in the elderly individuals. It may be affected, in part, by the attenuated hepatic albumin synthesis response to exercise [87, 88] due to decreased gene expression with normal aging. However, it is also reasonable that this is caused by insufficient protein intake for albumin synthesis in elderly people. Decreased daily activity with aging may be accustomed to low energy and protein diets in elderly people. Therefore, improvements would occur if substrates for plasma albumin synthesis are given immediately after exercise when albumin synthesis is reportedly enhanced [40, 88]. In this regard, one study showed that when young and elderly individuals ingested placebo (i.e., non-energy ingestion) just after acute high-intensity interval exercise, the ability of recovery of Alb_{cont} and PV after exercise was generally blunted in elderly individuals compered to young individuals. In contrast, Alb_{cont} and PV recovered more when they consumed a protein and CHO mixture compared to consumed placebo in both individuals [35].

Okazaki et al. [89] further determined the effects of protein and CHO intake just after exercise on PV and thermoregulatory responses during 8 weeks of aerobic training under cool to thermoneutral conditions in elderly individuals. In individuals consuming protein and CHO, Alb_{cont} and PV increased by 6%, and these increases were accompanied by enhanced sensitivities of SkBF and sweat rate (18 and 80%, respectively) to increased T_{es}. In contrast, they remained unchanged in individuals taking the placebo immediately after exercise [89].

Additionally, this enhanced sensitivity associated with a 10% increase in stroke volume during exercise [89]. Consequently, the improved PV expansion response induced by exercise along with post-exercise protein and CHO intake enhances the attenuated increase in cardiovascular and thermoregulatory capacity in elderly individuals compared with young counterparts. Recently, Kataoka et al. [90] reported the similar results in hypertensive elderly individuals (~160 mmHg for systolic and ~90 mmHg for diastolic blood pressure at rest) that PV and SkBF response to increased T_{es} both increased after aerobic training (60–75% of $VO_{2\,peak}$ for 60 min/day, 3 days/week, for 8 weeks) with protein (10 g) and CHO (15 g) supplementation. Furthermore, they showed that despite the increased PV, arterial blood pressures rather decreased after training with an increased carotid arterial compliance and baroreflex sensitivity.

Recent studies have presented that aerobic training improves cutaneous vasodilation by local mechanisms in aged skin [91]. Black et al. [92] used L-NAME (an NO synthase inhibitor) during acetylcholine infusions to block NO production and demonstrated that, in initially sedentary elderly individuals, increase in vascular responsiveness following 12 and 24 weeks of aerobic training was induced by the increase in action of NO in the skin. There are similar results in a longitudinal study [93] although a cross-sectional study reported no effects [94].

The enhancement of the sweating function in summer occurred later and its reduction in winter occurred earlier, in an elderly group compared with a younger group despite a smaller seasonal variation range [95]. To prevent heat disorders in elderly individuals, it is strongly recommended that they engage in exercise training prior to the summer season. Regular exercise generally improves thermoregulatory capacity alongside VO_{2max}. Protein and CHO intake after exercise will also enable adequate training adaptations to be achieved.

9. Effects of exercise training on thermoregulation in diabetic patients

The effects of aerobic fitness along with short- and long-term exercise training have been widely studied in the context of glucoregulation in type 2 and type 1 diabetics. The effects of exercise training on glycemic control in type 2 diabetics are well established. A recent meta-analysis by Umpierre et al. [96] reported that structured exercise training (over 12 weeks) consisting of aerobic exercise, resistance training, or a combination is associated with enhanced glycemic control (~0.7% HbA1c reduction) in type 2 diabetics. They also reported that structured exercise training of more than 150 min per week is associated with greater HbA1c reduction (~0.9%) compared to 150 min or less per week [96]. Structured exercise training also has beneficial effects on diabetes-related complications [97]. Greater benefits are apparent in type 2 diabetics with higher HbA1c before the exercise intervention [97].

In healthy individuals, it has been suggested that higher levels of aerobic fitness and/or physically activity improve the capacity to dissipate heat during exercise [98, 99]. A recent study indicated that the age-related decline in aerobic fitness was associated with the decreased whole-body evaporative heat loss during exercise in the heat [100]. Moreover, a group of trained middle-aged males (~48 years) exhibited greater whole-body heat loss than an untrained group during exercise [100]. Other studies have also indicated that VO_{2max} decreased ~7% per decade in sedentary, active, and even endurance-trained populations [101]. Despite reports of the relationship

between aerobic fitness and thermoregulatory capacity in healthy people, there are no reports in with either type 1 [102–104] or type 2 [71] diabetics because aerobic fitness has not been considered as a potential factor influencing thermoregulatory capacities. Therefore, the increased aerobic fitness with exercise training in diabetics would improve thermoregulatory control, autonomic nervous system function, and cardiovascular responses, especially during exercise-induced heat stress, as reported in healthy counterparts, however, the situation remains unclear.

10. Oral rehydration during exercise

Based on the physiological responses to warm and hot conditions described previously, it is suggested that dehydration prior to and during exercise should be prevented or countered. This would reduce extra thermal and cardiovascular strains during exercise in the heat and the risk of developing heat-related illnesses. In general, oral rehydration with solutions containing 0.1–0.2% of NaCl and 4–8% of CHO based on thirst sensation is recommended, but, during exercise, we need to prevent the addition of 2% of body weight reduction [7]. Elderly persons or persons who work or undertake high-intensity exercise in warm and hot conditions should start fluid ingestion prior to and during the early period of work before thirst is perceived [7]. Special care should be taken by diabetics so that hyper and hypoglycemia are not induced with oral rehydration during exercise and hyperthermic conditions.

11. Conclusions

The morbidity and mortality of heat-related illnesses would expand in the years to come worldwide because of the rapidly aging population and global warming. The decreased thermoregulatory capacity in type 2 diabetes is associated with the presence of neuropathies, reduced nitric oxide bioavailability, central mechanisms, and so on, while it would be improved with aerobic fitness with exercise training as in healthy counterparts. Thermoregulatory adaptations after exercise training are enhanced with PV expansion with a dietary supplementation conjunction with exercise in healthy individuals. Further researches are necessary to elucidate the effective strategy to improve thermoregulatory capacity as well as glycemic control in type 2 diabetes with or without complications with exercise training.

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