Meta-inflammation and cardiometabolic disease in obesity: Can heat therapy help?

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ABSTRACT

Obesity and associated metabolic dysfunction have reached epidemic proportions worldwide. The current theory linking metabolic disease and obesity involves ischemic adipose tissue initiating an inflammatory cascade that results in systemic insulin resistance and may eventually lead to type II diabetes mellitus. Diabetes and associated metabolic dysfunction increase the risk of developing cardiovascular disease and fatal cardiovascular events. By targeting key steps in this process, ischemia and inflammation, this cascade may be prevented or reversed and thus metabolic and cardiovascular health may be preserved in obesity. Regular heat exposure (termed ‘heat therapy’) offers potential to improve cardiometabolic health in obese individuals through a variety of mechanisms that include but are not limited to heat shock proteins, hypoxia-inducible factor 1α, and hemodynamic effects. The purpose of this review is to highlight the cardiometabolic decline in obese individuals stemming from adipose tissue dysfunction, and examine the ways in which heat therapy and associated cellular and systemic adaptations can intersect with this decline in function to improve or restore cardiovascular and metabolic health.

Obesity and associated disease rates have reached epidemic proportions, with nearly two billion people worldwide being classified as overweight or obese. For example, as of 2012, 33.7% of men and 36.5% of women in the United States were classified as obese (BMI ≥ 30), and 9.3% of the U.S. population suffered from type II diabetes, a disease closely associated with excess fat mass and a sedentary lifestyle. With rates of obesity and diabetes continuing to rise, these classifications are risk factors for the development of cardiovascular disease in both men and women. Thus, obese individuals are a high-risk population for both cardiovascular and metabolic disease (termed ‘cardiometabolic disease’), and interventions aimed at improving cardiometabolic health in obese populations are sorely needed. Current lifestyle interventions for obesity and cardiometabolic disease emphasize dietary modification and exercise training. While changing diet and exercise patterns can be effective strategies for reducing body mass, improving vascular health, and enhancing insulin sensitivity, compliance is often low in clinical populations. Barriers to exercise include physical limitations associated with obesity, injury, motivation, body image, and socioeconomic constraints. In extreme cases (morbid obesity, or obesity with comorbidities), surgical intervention through roux-en-Y gastric bypass, vertical sleeve gastrectomy, or other bariatric procedures is another technique to reduce excess mass and improve health. While weight loss is sustained and comorbidities are reduced in the majority of patients, this remains an expensive procedure with some patients continuing to deal with weight regain and/or unresolved diabetes, hypertension, and dyslipidemia.

Chronic heat exposure may offer an alternative or supplemental therapy to improve metabolic health and provide protection from cardiovascular disease in obese individuals. There are a variety of potential mechanisms for the observed improvements in cardiovascular and metabolic health with chronic, intermittent heat exposure (most commonly termed ‘heat therapy’, but also ‘hyperthermic conditioning’, or ‘thermotherapy’). The purpose of this review is to highlight the cardiometabolic decline in obese individuals.
individuals stemming from adipose tissue dysfunction, and examine the ways in which heat therapy and associated cellular and systemic adaptations can intersect with this decline in function to improve or restore cardiovascular and metabolic health. Finally, we review the current evidence of cardiometabolic improvement with heat therapy using different heating methods in humans.

**Obesity, inflammation, and insulin resistance**

While the growing obesity epidemic and associated metabolic disease rates have been well-documented and characterized, the causal link between obesity and metabolic dysfunction is continually being described and explored. Evidence points to an increase in systemic inflammation in obesity being a primary culprit in both metabolic and cardiovascular dysfunction. Early case studies noted improvement in diabetes mellitus and glycosuria with anti-inflammatory (salicylate) therapy, but no potential mechanism was proposed. In an animal model of obesity and diabetes, Hotamisligil et al. demonstrated that elevated systemic and adipose tissue tumor necrosis factor α (TNFα) abundance were associated with impaired glucose tolerance and adipocyte glucose uptake. In humans, obesity has since been found to be associated with higher levels of C-reactive protein, interleukin 6 (IL-6), fibrinogen, TNFα, plasminogen activator inhibitor 1, and several other inflammatory proteins. These proteins may be secreted by adipose tissue, liver, and skeletal muscle, and have implications in both metabolic and cardiovascular dysfunction. Weight loss through bariatric surgery, diet, or diet and exercise results in decreases in inflammatory markers including C-reactive protein, plasminogen activator inhibitor 1, IL-6, and TNFα. Additionally, anti-inflammatory therapy (salicylates) has been shown to reverse insulin resistance in obese rodents. These findings led to the current theory that inflammation drives obesity-induced insulin resistance.

The pathophysiological link between obesity and metabolic disease relates to increased triglyceride storage in adipocytes causing adipose tissue hypoxia through compression of capillary networks and inadequate blood supply relative to cell size. This initiates a cascade of adipocyte apoptosis, followed by a pro-inflammatory immune response (see Fig. 1). The immune response involves a variety of chemokines, adipokines, and immune cells, which alter the profile of obese adipose tissue to a pro-inflammatory phenotype. The change in immune cell profile includes an increase in M1 macrophages forming a crown-like structure around the adipocyte and releasing pro-inflammatory cytokines in the adipose tissue. Adipocytes act in a synergistic paracrine fashion with resident macrophages to increase inflammatory cytokine release by the other tissue. These cytokines are thought to disrupt insulin signaling in adipose tissue through serine phosphorylation of the insulin receptor substrate (IRS), which blocks tyrosine binding sites needed to activate the IRS within the cell and allow insulin signaling to occur. The primary function of insulin in adipose tissue is suppression of free fatty acid release, so the result of this impairment is increased fatty acids in circulation. These circulating fatty acids can accumulate in the liver and skeletal muscle and produce fatty acid intermediates such as diacylglycerol, ceramides, and long-chain fatty acid-Acyl CoA, all of which can inhibit intracellular insulin signaling by activation of c-Jun NH₂-terminal Kinase (JNK) or Inhibitor of kappa B kinase β (IKKβ). JNK and IKKβ similarly impair intracellular insulin signaling by serine phosphorylation of IRS. This results in systemic insulin resistance with an impaired ability of cells to transport glucose or suppress glucose production, creating a more metabolically inflexible profile. In addition, adipokines such as leptin and adiponectin are altered in obesity, with adiponectin in particular at much lower circulating levels in obese individuals. Adiponectin is positively correlated with insulin sensitivity, potentially acting by changing macrophage polarization toward an anti-inflammatory profile. The end result is a hyper-insulinemic and meta-inflammatory profile in obesity that vastly increases the risk of developing both metabolic and cardiovascular disease.

Within the central nervous system, inflammation and hyperinsulinemia are associated with increased sympathetic nervous system (SNS) outflow. IL-6 receptors are present on sympathetic ganglia and IL-6 infusions have been shown to increase SNS activity in humans. Further, elevated TNFα increases the expression of IL-6 receptors on sympathetic
neurons,30 and both cytokines are elevated in obese humans.33,34 Insulin also acts centrally to increase sympathetic outflow,35,36 increasing the risk of hypertension in insulin-resistant populations.37 High sympathetic outflow increases blood pressure through cardiac, renal, and arterial innervation, and SNS overactivity is considered an important risk factor for development of cardiovascular disease.38 In addition, obesity-induced SNS over-activity contributes to end-organ damage in the kidney, blood vessels, and heart, increasing cardiovascular morbidity and mortality, even in the absence of hypertension.39 Specific adipokines may influence the sympathetic overactivity,29 creating a vicious cycle of dysfunction that likely contributes to the cardiovascular and metabolic disturbances observed with obesity.

Systemic insulin resistance is also associated with impaired endothelium-dependent dilation and microvascular function,40,41 observed in impairment of insulin’s actions on blood vessels42 as well as reduction in bioavailable nitric oxide (NO) due to the high oxidative stress seen in hyperinsulinemic individuals.43 The meta-inflammatory state of obesity additionally causes impaired vascular remodeling, resulting in increased arterial stiffness44 and intima media thickness.45 Intima media thickening is also associated with the dyslipidemia seen in obesity throughout the lifespan.46

While all obese individuals are at an elevated risk of cardiometabolic dysfunction compared to healthy weight counterparts, there appears to be a sex difference, placing women with diabetes at an elevated risk for cardiovascular death as compared to obese, diabetic men.3 Within the population of obese women, diagnosis with polycystic ovary syndrome (PCOS) additionally carries a disproportionate risk of cardiovascular disease, diabetes, and cardiovascular death.47 PCOS is an endocrine disorder characterized by androgen excess, menstrual dysfunction, and polycystic ovaries upon ultrasound examination, and this syndrome affects up to 15% of women. The metabolic, autonomic, and hormonal profiles in women with PCOS greatly increase the risk for obesity, insulin resistance, and cardiovascular disease.48 Sympathetic over-activity49,50 may underlie the pathogenesis of PCOS and additionally increase risk of cardiovascular disease, so the potential for chronic heat to alter autonomic outflow is particularly promising in this population.

Figure 1. An overview of inflammation and ischemia in obese adipose tissue. Excess fat storage in obese individuals leads to adipose tissue expansion as compared to lean individuals, and the blood supply does not adequately match this tissue expansion. This adipocyte hypertrophy and inadequate blood supply causes adipocyte hypoxia, inflammatory cytokine release (IL-6, TNFα) by adipocytes and M1 macrophages, a reduction in adiponectin release, and impaired insulin action. Low adiponectin promotes the pro-inflammatory profile of macrophages, and adipocytes and macrophages act in a paracrine fashion to further increase cytokine release from neighboring adipose tissue. Insulin resistance in adipocytes causes impaired suppression of lipolysis, and fatty acids are released and deposited in other insulin target tissues such as skeletal muscle and liver. Partially oxidized fatty acids increase inflammation through proteins such as JNK and IKKβ in the liver and skeletal muscle, impairing insulin signaling in these tissues. Impaired insulin action in the liver leads to an increase in glucose release (impaired suppression of glycolysis), and in skeletal muscle leads to decreased glucose uptake (impaired GLUT-4 translocation). The end result is hyperglycemia, hyperlipidemia, meta-inflammation, and insulin resistance. Filled arrows with + signs represent increases in release or uptake, while unfilled arrows with − signs represent decreases in release or uptake.
How can chronic heat therapy help?

Regular heat exposure, through sauna use, hot water immersion, or combined exercise heat stress, is associated with a variety of cellular and systemic adaptations that have potential to improve cardiometabolic health in obese individuals. In animal work, passive heat exposure with marked elevation in core temperature is associated with changes in protein expression and abundance that lead to enhanced cardiovascular and metabolic health, as well as cellular protection from a multitude of stressors.\(^51,52\) Long-term passive heat acclimation (30 days) has been shown in animal models to initiate cellular pathways such as Heat Shock Proteins (HSP) and Hypoxia-inducible Factor \(1 \alpha\) (HIF1\(\alpha\))\(^51,52\) that enhance blood supply, protect cells from stressors such as ischemia,\(^53\) and reduce inflammation.\(^54\) In addition, altered expression of adipokines such as leptin and adiponectin have been observed in animals following repeated heat exposure.\(^55\) As such, there are multiple possible mechanisms by which heat therapy in humans could attenuate or prevent the development of insulin resistance, diabetes, and cardiovascular disease in obesity. These mechanisms may work synergistically to intersect with the obesity-inflammation cascade to potentially reduce ischemia, inflammation, insulin resistance, and vascular dysfunction.

Ischemia, inflammation, and insulin resistance

Seminal work in animals using long-term heat acclimation first described heat acclimation cross-tolerance, where long-term passive heat acclimation protected cells from a multitude of stressors, including ischemia/hypoxia. This was first described in the rat heart, with a reduced infarct size in response to ischemia-reperfusion injury in heat-acclimated animals.\(^53\) Since then, interest in heat/hypoxia cross-tolerance has expanded\(^56\) to include acute human studies of ischemia-reperfusion\(^57\) and human performance models.\(^58,59\) It is thought that both HSPs and HIF1\(\alpha\) play a role in protection from ischemic injury.\(^52\)

In obesity, adipocyte ischemia is among the first steps leading to cardiometabolic dysfunction. Chronic heat provides multiple avenues to improve blood supply (see Fig. 2). For example, one downstream target of HIF1-\(\alpha\) is vascular endothelial growth factor (VEGF),\(^53\) which stimulates microvascular angiogenesis. Recent human work examining acute heat exposure demonstrated increased expression of various angiogenic signals including VEGF and angiopoietin after one 90-minute leg heating session, with concomitant increases in Hsp90 expression.\(^60\) Hsp90 can also act through stabilizing endothelial nitric oxide synthase,\(^61\) and NO acts as another angiogenic signal.\(^62\) In addition, NO production in endothelial cells is enhanced through shear stress,\(^63\) as observed during acute heating. If blood supply to adipocytes is improved through some combination of these mechanisms, adipocytes are less likely to become ischemic, which may attenuate the inflammatory response that comes from ischemia-induced hypoxia. While acute heat exposure may result in transient increases in pro-inflammatory compounds such as IL-\(6\) and JNK,\(^65\) chronic heat treatment has been shown to decrease intracellular levels of inflammatory proteins such as JNK and IKK\(\beta.\(^66\)\)

Heat shock proteins have been linked with altered expression of pro- and anti-inflammatory cytokines\(^67,68\) and decreases in other inflammatory compounds such as JNK and IKK\(\beta\) in skeletal muscle\(^66\) in response to repeated heat exposure. IL-6 and TNF\(\alpha\), both targets of HSPs, are associated with impaired insulin signaling in adipose tissue,\(^69–71\) and JNK and IKK\(\beta\) have been shown to impair insulin signaling in skeletal muscle, as well as liver and adipose tissue.\(^21,72,73\)

HSP levels have been linked to insulin sensitivity in humans\(^74\) through a variety of mechanisms. Individuals with type II diabetes exhibit reduced levels of HSPs in adipose tissue\(^75\) and skeletal muscle.\(^74\) Animal work using regular heat exposure examined the relationship between various HSPs and insulin signaling in rat skeletal muscle, and found both Hsp27 and Hsp70 decreased inflammatory proteins such as JNK and IKK\(\beta\), both known to impair insulin signaling through serine phosphorylation of IRS-1.\(^66\) In adipose tissue, Hsp70 decreases the expression of nuclear factor kappa-B, which in turn reduces the release of pro-inflammatory cytokines such as IL-1\(\beta\), IL-6, and TNF\(\alpha\).\(^76\) Hsp70 is additionally involved in the protein refolding of the insulin receptor when denatured by stress,\(^77\) providing another mechanism through which heat shock proteins can improve or maintain insulin signaling in populations with impaired metabolic health. In skeletal muscle, mild heating increases expression of genes encoding mitochondrial biogenesis,\(^78\) which can increase energy flux in the cell and reduce the accumulation of the fatty acid intermediates linked to inflammation and
insulin resistance. In addition, animal work has suggested that as little as five days of passive heat exposure in mice increased serum adiponectin levels, which is associated with enhanced insulin sensitivity and reduced inflammation.25

Vascular dysfunction

In advance of overt cardiovascular disease, obesity and insulin resistance can increase cardiovascular dysfunction and blood pressure through impaired vascular remodeling,25,79 endothelial dysfunction,40 and elevated sympathetic nervous system activity.29,80 While the relative contributions of obesity, inflammation, and metabolic dysfunction are difficult to tease apart, these elements combine to create an elevated risk of cardiovascular disease and cardiovascular death3 in obesity.

Heat therapy offers potential to attenuate or reverse impairment through a variety of mechanisms (see Fig. 3). First, acute heating, through hot water immersion or sauna, promotes increases in cardiac output and redistribution of blood flow to the periphery as a cooling mechanism. This increase in skin blood flow alters the shear pattern of arterial blood flow through conduit vessels to increase anterograde shear and reduce retrograde shear.63,81,82 This altered shear pattern has been shown to enhance vascular remodeling and endothelial function following exercise training83,84 and passive heating.81,83 Acute leg heating has also been shown in patients with symptomatic peripheral artery disease to enhance lower limb blood flow, reduce blood pressure and decrease circulating endothelin-1,85 all of which can improve vascular health and function, particularly if heat is repeatedly applied over time.

Heat shock proteins also play an important role in cardiovascular protection. In vascular remodeling, Hsp27 reduces intimal hyperplasia,86 an early step in formation of atherosclerotic plaques. Hsp72, through inhibition of Angiotensin II, reduces vascular smooth muscle hypertrophy.87 Heat exposure has additionally been associated with reductions in IL-688 and increases in adiponectin,55 which promote and inhibit vascular inflammation, respectively.

Endothelial function, in healthy populations, is predominantly dependent on the production of bioavailable NO.89 Hsp90 is an essential cofactor for nitric oxide synthase stability,61 so increases in Hsp90 expression would likely lead to an increase in endothelial NO production, as seen in animal models.90,91 In human models of vascular function, this increased...
NO production would enhance vasodilation as assessed by techniques such as flow-mediated dilation and cutaneous local heating. Since endothelial and cutaneous microcirculatory function are impaired in obesity, even in advance of overt cardiovascular disease or hyperglycemia, improving microcirculatory function is a promising means to improve cardiovascular health in obese individuals.

Sympathetic nervous system activity is regulated through a variety of neurological, neurohumoral, and psychological inputs, and can be modulated by a variety of hormones and compounds including adiponectin, Angiotensin II, and NO. In addition to the cardiovascular consequences of high sympathetic activity, sympathetic outflow is inter-related with metabolic function in obesity. High circulating epinephrine suppresses insulin release from the pancreas and increases lipolysis and fatty acid release in to the bloodstream. In turn, inflammation and hyperinsulinemia increase sympathetic outflow, creating a positive feedback loop for both cardiovascular and metabolic decline in obesity. Chronic heat exposure offers potential to reduce sympathetic outflow through reductions in inflammation and insulin resistance as previously described, and can additionally reduce sympathetic activity through increasing circulating adiponectin and enhancing NO production. Heat acclimation has additionally been shown, in murine models, to increase Angiotensin II receptor subtype 2 (AT2) in the hypothalamus, which acts to reduce sympathetic outflow.

In combination, heat therapy offers the potential to improve metabolic and cardiovascular function and risk through a variety of mechanisms. To date, research in humans, particularly in obese individuals, has been limited.

**Current evidence in humans**

A variety of heating methods, timelines, and cardio-metabolic outcome measures have been examined in healthy and obese populations. Hot water immersion was one of the first therapeutic methods to be studied in humans, with Hooper examining glucose control in eight obese, diabetic individuals following three weeks of regular hot tub use (30 minutes per session). The subjects experienced a large decrease in fasting glucose and glycosylated hemoglobin, and the
researchers postulated that this was due to the increased blood flow to skeletal muscles during heating. While multiple alternative mechanisms have since been explored, this study was among the first to examine health benefits of passive heating in obese individuals. Local heating of abdominal adipose tissue, similar to that experienced during hot water immersion, has also been shown to reduce visceral fat storage and improve glucose tolerance in obese, diabetic individuals.103

Acute hot water immersion has since been studied as a means to improve glucose control. Faulkner and colleagues64 compared the glucose response to a meal after either a 60-min hot bath or 60-min moderate intensity exercise in lean and overweight men, and found that heat decreased peak post-prandial glucose compared to exercise, with no difference in 24-h glucose control between heat and exercise. The authors postulated that increased HSP production in response to heat drove the improved glucose control through enhanced insulin signaling.

Vascular health and function have also been examined in response to repeated passive heat exposure in healthy, inactive men and women. Brunt and colleagues92 examined the effect of 8 weeks of hot water immersion (4–5 times per week for ∼90 min per session, with core temperature increase of ∼1.5°C) and observed improvements in endothelial function, arterial stiffness, wall thickness, and blood pressure. In a companion study, this group also investigated cutaneous vasodilation in response to local heating as a model of microvascular function and specifically examined the role of NO,93 and observed an increase in cutaneous vascular conductance to thermal hyperemia that was primarily mediated by NO.

Sauna has also been investigated both as an intervention in clinical populations and in prospective cohort studies. Classic Finnish saunas involve air temperatures of 80–100°C with low humidity, and individuals spend 5–30 minutes at a time in the sauna with brief breaks in a thermoneutral room between multiple bouts. A 30-min bout in an 80°C sauna quickly increases skin temperature and heart rate, and raises rectal temperature ∼0.9°C.104 Two weeks of thermal therapy (60°C far-infrared sauna 6 days per week) in men with elevated cardiovascular risk significantly improved endothelial function, assessed via flow-mediated dilation.105 A study in men with congestive heart failure underwent the same therapy and similar improvements in flow-mediated dilation were observed.106 In addition, brain natriuretic peptide (a marker of cardiac dysfunction) was significantly reduced following thermal therapy.

A large prospective cohort study (2,315 Finnish men) examined frequency and duration of sauna use and the correlation with mortality rates during a 20-year follow-up.107 Increased frequency and duration of sauna use were associated with substantially reduced hazard ratios for sudden cardiac death, fatal coronary heart disease, fatal cardiovascular disease, and all-cause mortality. While this study only examined men, did not include subject that did not regularly use sauna, and did not specifically examine death related to metabolic diseases such as diabetes, it is the largest and longest study to date on the potential long-term cardiovascular health benefits of regular passive heat exposure.

Performing yoga in a hot room may offer an alternative to passive immersions in more able-bodied populations, with the additional benefit of low to moderate intensity exercise. Research is mixed on the increase in core temperature observed during a 90-min Bikram yoga class (a series of 26 postures in a room set to 40.5°C, 40% relative humidity), with values ranging from mild hyperthermia [0.6–1.0°C] to increases more similar to those seen in hot water immersion [1.7–2.5°C] in men and women, respectively108 to increases more similar to those seen in hot water immersion [1.7–2.5°C] in men and women, respectively109]. While core temperature elevation in hot yoga is highly dependent on both ambient temperature and level of intensity (metabolic heat production), some promising results of hot yoga training have been seen in obese populations.

Hunter et al.110 examined the effect of an 8-week hot yoga intervention (three 90-minute sessions per week) on body composition and glucose tolerance. Following this intervention, a significant reduction in glucose area under the curve was noted in obese men and women, with no change in lean individuals. Fasting glucose did not change in either population, and body composition was additionally unaltered. Since this study did not have an exercise-only, heat-only, or time control, it is unclear whether the exercise, the high temperature, or the combination of both stressors drove these changes. However, the findings do suggest that hot yoga may improve glucose tolerance in obese individuals.

In a similar intervention study from the same research group, arterial stiffness, blood pressure,
cholesterol, and insulin levels were examined in healthy younger and older individuals in response to an 8-week Bikram yoga practice.\textsuperscript{111} Again, this study lacked a control group to tease apart the effects of yoga, heat, or time, but younger individuals experienced a decrease in arterial stiffness, while older individuals experienced a decrease in fasting insulin and low-density lipoprotein-cholesterol. Blood pressure did not change in either group after the 8-week Bikram yoga intervention.

Guo et al\textsuperscript{112} performed a longer-duration study examining markers of body composition, cardiovascular health, and psychological well-being follow one year of Bikram yoga (4 sessions per week) in obese individuals. The yoga intervention led to significant reductions in skinfold thickness, waist circumference, blood pressure (MAP decreased $\sim 3$ mmHg), total cholesterol, low-density lipoprotein-cholesterol, and triglycerides, and led to increases in vital capacity, high-density lipoprotein-cholesterol, and subjective scores of well being. No study has yet examined the combination of metabolic and cardiovascular health markers following hot yoga training, but these early studies suggest a benefit for cardiometabolic health in obese populations.

### Summary & perspectives

The multifaceted decline in cardiovascular and metabolic function that occurs in obesity has been well-described, and despite treatment options including diet, exercise, surgery, and a variety of medications, obesity remains a global epidemic with extremely high associated healthcare costs.\textsuperscript{113} Chronic heat exposure as heat therapy offers potential as a novel or adjunctive therapy to improve cardiometabolic health in obesity and to potentially reduce the medical burden of obesity. While not offering a direct path to weight reduction, the reductions in inflammation, improvements in glucose tolerance, and improvements in vascular function that have been observed in human and animal models with chronic heat exposure provide a variety of avenues through which cardiometabolic health can be improved in the absence of weight changes.

Future work exploring heat therapy as a means to improve cardiometabolic health should examine a dose-response and timeline, as a wide variety of acute and chronic timelines have been utilized, resulting in a large range of core temperature responses, and total heat exposure time ranging from 9 hours over 3 weeks\textsuperscript{102} to over 300 hours in a 1-year intervention.\textsuperscript{112} The underlying mechanisms to explain the observed health benefits also require further study in humans, with blood samples, tissue biopsies, and complementary cell work providing promising avenues for exploration of changes in protein abundance, gene transcription, and downstream targets. In addition, more work is needed examining passive heat in at-risk and understudied populations, including obese women with or without PCOS, and those at increased cardiometabolic risk but with limited ability to gain the full benefits of exercise, such as individuals living with spinal cord injury.

### Abbreviations

- AT2: angiotensin II receptor subtype 2
- HIF1$\alpha$: hypoxia inducible factor 1$\alpha$
- HSP: heat shock protein
- IKK$\beta$: inhibitor of kappa B kinase $\beta$
- IL-6: interleukin-6
- IRS: insulin receptor substrate
- JNK: c-Jun NH2-terminal kinase
- NO: nitric oxide
- PCOS: polycystic ovary syndrome
- SNS: sympathetic nervous system
- TNF$\alpha$: tumor necrosis factor $\alpha$
- VEGF: vascular endothelial growth factor

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