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Is exercise an effective therapy for menopause and hot flashes?

Hot flashes and night sweats are the main physical symptom of menopause[1]. Most women (particularly in North American and European countries) experience hot flashes for on average 5 years during menopause, with some women reporting symptoms for up to 10 years[1,2]. Hot flashes and the acute onset of perspiration and increased skin blood flow (i.e., flushing) can be accompanied by other cardiovascular responses (i.e., an acute drop in blood pressure and brain blood flow[3,4]) as well as sensations of hot and cold, perspiration, anxiety, frustration, depression, light headiness and nausea[5-7]. Such symptoms can significantly reduce the quality of life for symptomatic women[8], and therefore appropriate and effective treatment is needed. Hormone therapy (HT) or prescribed medications for specific menopause symptoms (i.e., anti-depressants) are the main treatment options clinicians can recommend to symptomatic women. Yet given the prevalence, duration and impact of menopausal symptoms, the effectiveness of alternative treatments (whether used instead or in conjunction) warrants careful consideration and investigation; particularly for women reluctant or contraindicated to use HT (i.e., women with a history of breast cancer, ovarian cancer, or cardiovascular disease).

Exercise is the most accessible, effective and safe intervention to improve and maintain general health as well as treat many lifestyle-induced chronic diseases[9,10]. Both continuous moderate-intensity and high-intensity interval exercise training elicits a plethora of metabolic, endocrine, cardiac and vascular adaptions that enhances cardiorespiratory/ metabolic function and health. Additionally, resistance exercise training enhances skeletal muscle mass, strength, power, and activation as well as bone mineral density. Thus, the general health benefits of regular strenuous physical activity (i.e., exercise) are well accepted[11]; though the optimal dose-response relationship has yet to be established between these beneficial adaptations and various parameters of exercise (mode/intensity/ frequency/duration)[9].

While exercise training induces both short and long-term health benefits, the effects of exercise on menopausal symptoms, particularly hot flashes, remains equivocal. Observational studies have associated high levels of exercise with a lower hot flash frequency and the reverse with sedentarism[12]. However, randomized controlled trials have found that aerobic exercise interventions (ranging from 12 weeks to 12 months) do not

improve hot-flash symptoms; though exercise was found to positively influence insomnia, subjective sleep quality, depressive symptoms, and memory problems in menopausal women[13,14]. The lack of causality between exercise training and reduced hot flash frequency/severity is perhaps surprising given that a key causal factor for hot flashes has been attributed to reductions in estrogen and associated thermoregulatory and vascular dysfunction. Certainly, short-term endurance training enhances thermoregulation in men and women by way of lowering resting body core temperature, decreasing body temperature thresholds for heat loss responses (i.e., activating sweating and increasing skin blood flow at lower body temperatures) and increasing sweat sensitivity (i.e., increasing sweat output per unit change in body temperature)[15,16]. Such thermoregulatory adaptations enhance thermoregulatory control and body core temperature regulation during exercise. Yet, the direct causality between exercise training, the thermoregulatory control system, and hot flash vasomotor symptoms has until now not been examined.

The study by Bailey et al.[17]published in the current issue of Menopause has for the first time tested this hypothesis by investigating if improved thermoregulatory control and vascular function via an exercise intervention alleviates hot flashes. They found that a 16-week exercise training intervention significantly reduced hot flash weekly frequency by ~62% in their exercise cohort (n=14 symptomatic women). Reductions in hot flash frequency and severity corresponded to a lower resting body core temperature, decreased body temperature thresholds for the onset of heat loss responses as well as an increase sweat sensitivity in the exercise cohort, as compared to a control group (n=7 symptomatic women). These findings raise interesting questions regarding the management of hot flashes and our understanding of their underpinning mechanisms. It could be suggested that lower body temperature thresholds for heat loss responses and increased sweat sensitivity might exacerbate hot flash severity and/or frequency. Indeed, a cross-sectional study has shown that symptomatic women have lower body temperature sweating thresholds and higher maximal sweat rates than age- and weight-matched asymptomatic postmenopausal women[18]. In connection to this, it has been hypothesised that a narrowing of the thermoregulatory zone (i.e., the homeostatic body temperature range wherein thermoregulatory responses are not triggered) underlies hot flash incidence in symptomatic women[19]. Meaning that during menopause, neurally-driven changes in thermoregulatory

control causes symptomatic women to sweat and increase skin blood flow at lower body core temperatures and shiver plus decrease skin blood flow at higher body core temperatures[19]. Thus, an earlier onset of heat loss responses due to exercise training could further exacerbate an already narrowed thermoregulatory zone and determine that hot flashes trigger more readily. However, exercise training-induced decreases in body temperature thresholds for heat loss responses should be offset by a lower resting body core temperature. This appears to be the case in the Bailey et al.[17] exercise cohort, where exercise training-induced decreases in resting body core temperatures matched the reduction in body temperature thresholds for heat loss responses. Thus, it appears that exercise training shifted the thermoregulatory set points of symptomatic postmenopausal women, though it remains to be seen if such changes affect the full thermoregulatory zone. It is also unknown how exercise training and changes in sweat rate (i.e., the number of activated sweat glands and/or sweat output per gland) might affect thermal sensation and comfort in postmenopausal women and thus influence self-reports of hot flash frequency/severity.

The menstrual cycle has a profound effect on vasomotor and thermoregulatory responses. It is well known that body core temperature changes over the course of the menstrual cycle, increasing ~0.5°C during the luteal phase[20]. Female sex hormones also influence skin blood flow and sweating. Notably, unopposed progestin (administered via contraceptive pills) increases body core temperature and delays the onset of heat loss responses, the converse occurring with estrogen *and* progestin treatment[21]. Further, HT administering only estrogen to postmenopausal women has been shown to lower body core temperature and body temperature thresholds for heat loss responses, with combined estrogen and progestin administration removing such effects[22]. Thus (perhaps unsurprisingly), estrogen or the absence thereof, has a central role in thermoregulatory responses and menopausal hot flash symptoms. Significantly, it appears that appropriate exercise training can elicit similar thermoregulatory adaptations as HT. Further, these adaptations appear to occur independent of circulating levels of female sex-hormones[15]. Thus, it seems thermoregulatory adaptations (i.e., lowered resting body core temperature and lowered onset of sweating and skin blood flow responses) can alleviate hot flash symptoms, whether they are achieved via endurance training or HT. Further work to

elucidate the mechanisms by which this occurs as well as potential complementary or augmented effects from exercise and HT treatments seem warranted.

Why then have previous exercise intervention studies[13,14] found that an exercise intervention does not alleviate hot flash frequency/severity? An important clarification to make for any exercise intervention is the level of stimulus and the related desired adaptation. Notably, for endurance training to improve heat loss responses, aerobic fitness (as indicated by maximal oxygen consumption) must increase by 15-20%[23]. Thus, for an exercise intervention to affect hot flash vasomotor symptoms, it must be of a suitable intensity to improve aerobic fitness and underlying cardiovascular responses. One explanation for the conflicting findings in the literature to date is that the exercise training stimulus used in earlier intervention studies may have been too moderate to confer significant thermoregulatory changes; in particular, a lower body core temperature (for example, Aiello et al.[14] exercise intervention only increased maximum oxygen consumption by ~13% (95% confidence interval: 8.8-14.6%)). Future exercise intervention studies must consider this and ensure an adequate increase in maximal oxygen consumption to see associated improvements in heat loss responses. Prospective studies might also consider how other cardiovascular and thermoregulatory responses (i.e., sweat gland activation, blood volume, neurotransmitter changes etc.) are linked to hot flash frequency/severity and thus begin to ascertain the optimal exercise dose-response to mitigate hot flashes in symptomatic women. Though, it is worth highlighting that even if hot flash symptoms are not alleviated by an exercise intervention, there are <u>many</u> other positive health benefits associated with exercise that will benefit menopausal women (e.g., increased/maintained bone density and muscle mass, reduced adiposity, improved blood lipid profile etc.).

In conclusion, further evidence is required to understand how exercise could alleviate menopausal symptoms, in particular hot flashes. Though earlier randomize control trials have shown that exercise does not improve hot flash ratings, this may be in part due to the magnitude of the exercise stimulus and a lack of thermoregulatory adaptation. Interesting, HT in postmenopausal women elicits similar thermoregulatory responses as exercise training, with an associated reduction in hot flash ratings. Thus, hot flash frequency in addition to severity appear to be reduced by lowering resting body core temperature, decreasing body temperature thresholds for heat loss responses and increasing sweat and

skin blood flow sensitivities. However, the optimal exercise dose or physical conditioning strategy has yet to be identified. Thermoregulatory changes and hot flash symptoms appear to be centrally mediated, though how changes in estrogen affect thermoregulatory centers in the brain has not been fully elucidated.

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