Elevating body temperature to reduce chronic low-grade inflammation: a welcome strategy for those unable to exercise?

Sven P. Hoekstra[1,2], Nicolette C. Bishop[1], Christof A. Leicht[1,2]

[1] School of Sport, Exercise, and Health Sciences; Loughborough University; Loughborough; UK
[2] The Peter Harrison Centre for Disability Sport; Loughborough University; Loughborough; UK

Abstract

Chronic low-grade inflammation is increasingly recognised in the aetiology of a range of chronic diseases, including type 2 diabetes mellitus and cardiovascular disease, and may therefore serve as a promising target in their prevention or treatment. An acute inflammatory response can be induced by exercise; this is characterised by the acute increase in pro-inflammatory markers that subsequently stimulate the production of anti-inflammatory proteins. This may help explain the reduction in basal concentrations of pro-inflammatory markers following chronic exercise training. For sedentary populations, such as people with a disability, wheelchair users, or the elderly, the prevalence of chronic low-grade inflammation-related disease is further increased above that of individuals with a greater capacity to be physically active. Performing regular exercise with its proposed anti-inflammatory potential may not be feasible for these individuals due to a low physical capacity or other barriers to exercise. Therefore, alternatives to exercise that induce a transient acute inflammatory response may benefit their health. Manipulating body temperature may be such an alternative. Indeed, exercising in the heat results in a larger acute increase in inflammatory markers such as interleukin-6 and heat shock protein 72 when compared with exercising in thermoneutral conditions. Moreover, similar to exercise, passive elevation of body temperature can induce acute increases and chronic reductions in inflammatory markers and positively affect markers of glycaemic control. Here we discuss the potential benefits and mechanisms of active (i.e., exercise) and passive heating methods (e.g., hot water immersion, sauna therapy) to reduce chronic low-grade inflammation and improve metabolic health, with a focus on people who are restricted from being physically active.

Keywords: hyperthermia, passive heating, cytokines, heat shock protein, glucose metabolism

Corresponding author:
Christof A. Leicht, c.a.leicht@lboro.ac.uk

Chronic low-grade inflammation and chronic disease

Introduction

Type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD) are associated with small, yet sustained elevations in circulating levels of pro-inflammatory proteins, a state called chronic low-grade inflammation (11). Causative links between inflammation and the aetiology of those diseases have been suggested (34). For example, in T2DM, chronically elevated plasma concentrations of pro-inflammatory cytokines can impair insulin sensitivity by affecting insulin signalling, potentially through inhibition of C-Jun N-Terminal Kinase (JNK) (72). Indeed, it has been shown that attenuation of JNK activity is associated with protection from insulin resistance in mice (63). For CVD, vascular integrity may be impaired by pro-inflammatory cytokines, facilitating the infiltration of macrophages through the vascular wall to form atherosclerotic plaques (9). Gene knockout studies in mice provide experimental evidence that the actions of tumour necrosis factor α (TNF-α) lead to an increase of plaque formation (19). This aligns with observational epidemiological data that show a positive association between pro-inflammatory markers and future CVD events (147).

These examples indicate that targeting inflammatory pathways might help to prevent and treat chronic inflammatory diseases. The last two decades have seen a host of studies investigating the anti-inflammatory effects of lifestyle interventions, such as exercise (54). Inflammation is multi-faceted in nature. Here we introduce two categories of inflammatory markers that are relatively well studied in the context of exercise, temperature and chronic low-grade inflammation: cytokines and heat shock protein. Referring to literature focused on exercise in addition to passive heating, we then discuss how temperature can affect chronic inflammation, providing rationale for the potential benefits of elevated temperature in chronic disease prevention.

Cytokines

It is recognised that a surplus of body fat is an independent risk factor for T2DM and CVD (151). Confirming the interactions between obesity and inflammation, it has been demonstrated that basal circulating interleukin (IL)-6 concentration in obese individuals is elevated, and that weight loss can reduce the concentration of this risk marker (32, 96). A mechanistic explanation lies in visceral adipose tissue and the residing macrophages within that are a major source of circu-

lating IL-6 at rest (11). Further mechanistic evidence is derived from the associations between obesity, increased intestinal permeability and inflammation (125). Both a high fat diet and increases in body mass increase intestinal bacterial species' DNA in adipose tissue, which correlates with TNF-α mRNA expression in adipose tissue (2). The importance of inflammatory pathways in the aetiology of T2DM is further underlined by data demonstrating that inhibition of pro-inflammatory pathways by knocking out the nuclear factor kappa B (NF-κB) (5) and JNK (65) pathways disrupts the link between obesity and insulin resistance in obese mice. In addition, pro-inflammatory cytokines can prevent tyrosine phosphorylation of IRS-1 upon activation of the insulin receptor and instead promote phosphorylation of IRS-1 on its serine residues, which leads to impaired insulin signalling (72). This might explain why blocking the actions of pro-inflammatory cytokines using anti-TNF-α treatments can improve insulin sensitivity (73).

The cytokine interleukin (IL)-6 has been extensively studied in the context of chronic low-grade inflammation; however, to date, its causative role remains heavily debated (34, 121). Observational studies report a positive association between the chronic elevation of plasma IL-6 concentration and insulin resistance, atherosclerosis, T2DM and CVD (11, 34, 38, 120, 144), linking it with chronic disease. It is important, however, to appreciate the diverse actions of IL-6. For instance, infusion of IL-6 for 2 to 4 h does not alter (133) or even enhances insulin sensitivity (25). There are possible explanations for this discrepancy. Whereas transient increases in plasma IL-6 concentrations can acutely enhance insulin action via AMP-activated protein kinase activation and glucose transporter-4 (GLUT4) translocation (25), chronic increases may impair insulin signalling by inhibiting the phosphorylation of tyrosine residues on IRS-1 (34). In the context of T2DM, it is noteworthy that IL-6 production is upregulated in response to increased concentrations of TNF-α (135). Because the detrimental role of TNF-α in insulin sensitivity and vascular function is relatively well-established (34, 135), it has been suggested that IL-6 may serve as a bystander rather than having a direct impact on health (43). On the other hand, pharmacological blocking of the IL-6 receptor can alleviate symptoms of a range of inflammatory diseases, such as rheumatoid and juvenile idiopathic arthritis (76). However, this also brings about increased concentrations of cholesterol and worsening of insulin sensitivity (117). The exact function of IL-6 in the circulation may also depend on the receptors it binds to following appearance in the circulation. Several cell types (e.g., leukocytes, hepatocytes) express surface IL-6 receptors for *classic* IL-6 signalling, while IL-6 can also bind to soluble IL-6 receptors present in the circulation, after which the resulting complex can bind to cells that do not express the IL-6 receptor (e.g., skeletal muscle cells) in a process called trans-signalling. It is the latter signalling pathway that is suggested to be mainly associated with inflammation (53). Taken together, although the exact underlying mechanisms need further research, chronically elevated plasma IL-6 concentrations are associated with poor metabolic health (11, 34).

Monocytes contribute to the inflammatory profile as they are producers of pro-inflammatory cytokines by signalling through their surface receptors, toll-like receptor (TLR)2, TLR4 and cluster of differentiation (CD) 14 (1, 7). By binding to the TLR-CD14 complex, pathogen-associated molecular patterns can trigger the production of cytokines such as IL-6 and TNF-α through the activation of the NF-κB pathway (7). As a result, the expression of TLRs on the surface of monocytes has been suggested to be a marker for chronic-low grade inflammation (89), particularly TLR2 and TLR4 (47). Indeed, monocytes from individuals with T2DM express more TLR2 and TLR4 when compared with healthy controls (35).

In addition to the surface expression of TLRs, the inflammatory nature of monocytes can be characterised by their expression of CD14 and CD16. Using these two surface markers, monocytes can be divided into three subsets: classical monocytes ($CD14^{++}CD16^{-}$), intermediate monocytes ($CD14^{++}CD16^{+}$) and non-classical monocytes ($CD14^{+}CD16^{++}$) (154). Interestingly, TLR4 expression is lowest in the classical subsets, as shown in patients with acute myocardial infarction (78) or stable angina pectoris (116). This might explain why a large proportion of intermediate and non-classical monocytes are associated with CVD, T2DM and other chronic diseases (103, 153), suggesting that the distribution of monocyte subsets can be used as a marker for chronic low-grade inflammation. Indeed, in response to an *in-vitro* stimulant (i.e., lipopolysaccharide (LPS)) non-classical and intermediate monocytes produce more of the pro-inflammatory cytokines TNF-α and IL-1β than the classical subset (17, 110).

Heat shock protein

The presence of heat shock protein (HSP) has been confirmed in every eukaryotic cell type and HSP subtypes have been defined based on their molecular mass, ranging from the HSP10 to the HSP110 family. Notably, contrary to what the name might suggest, HSPs are not exclusively induced by heat but are responsive to a range of stressors including hyperthermia, oxidative stress and glycogen depletion (112). With regards to chronic low-grade inflammation, exercise and temperature, the HSP70 family, with its inducible subtype Hsp72, is most widely studied and is the HSP of focus in this review. Note that we use the nomenclature adopted by the Cell Stress Society International, in which HSP refers to the protein family, Hsp refers to the specific protein, and *hsp* refers to the gene and mRNA expression.

Intracellular Hsp72 (iHsp72) functions as a chaperone for protein folding and aids in the maintenance of homeostasis within cells (112). Indeed, the survival rate in mice subjected to heat shock is higher when iHsp72 expression is elevated by a prior non-lethal heat shock compared to control mice (84). When in homeostasis, Hsp72 is bound to heat shock factor-1 (HSF-1) in the cytosol, rendering this complex inactive. In response to physiological stress or inflammation, these molecules are uncoupled, allowing HSF-1 to translocate to the nucleus and activate heat shock elements on the heat shock protein gene. As a result, the transcribed *hsp72* mRNA then leads to an increased Hsp72 protein expression in the cytosol (82). Expression of Hsp72 and its association with metabolic health has been assessed in a variety of cell types, with levels in

leukocytes, adipose tissue and skeletal muscle tissue having gained most attention in the context of chronic low-grade inflammation and metabolic health (63). It is suggested that iHsp72 exerts its anti-inflammatory actions by blocking the activity of the JNK and NF-κB pathways, reducing the production of pro-inflammatory cytokines and enhancing insulin sensitivity (30, 63). Indeed, it has been shown in cell culture experiments that JNK activation is reduced in cells overexpressing Hsp72 (48), and that a high iHsp72 expression prevents the activation of NF-κB and subsequent TNF-α gene transcription (106).

A growing body of evidence supports the importance of HSP in the aetiology of T2DM and CVD (63, 71). In humans, iHsp72 expression in skeletal muscle and adipose tissue is lower in those with T2DM and non-alcoholic fatty liver disease when compared with healthy controls (20, 24, 62). In murine models, Hsp72 knock-out mice develop insulin resistance and obesity (63), and mice in which iHsp72 is overexpressed are protected against the deleterious effects of high fat overfeeding on insulin sensitivity (61). Protection from insulin resistance in mice appears to be associated with the attenuation of JNK. Interestingly, in this particular study JNK attenuation was achieved by heat therapy (63). Moreover, pharmacologically restoring Hsp72 expression induces an 85% increase in glucose clearance rate during intravenous glucose infusion in Hsp72-deficient monkeys (80).

Whereas animal studies have provided compelling evidence of the influence of iHsp72 in skeletal muscle on metabolic health (30, 80), the protective effect of an elevated expression of iHsp72 in immune cells is less clear. Compared with other leukocyte subsets, iHsp72 in monocytes is most responsive to stress and iHsp72 expression shows a dose-response relationship with incubation temperature in isolated cell suspensions (8). Monocytes produce a range of pro-inflammatory cytokines when activated including TNF-α and IL-1β (36); iHsp72 expression in this cell type may therefore directly affect the inflammatory profile of an individual. In addition, and similar to skeletal muscle, monocytes are insulin-sensitive. Their behaviour may therefore serve as surrogate measure for peripheral insulin sensitivity (128). Simar et al. (129), Singh et al. (130) and Njemini et al. (111) found a reduction in resting iHsp72 expression in monocytes as a result of ageing, a process associated with the development of chronic low-grade inflammation (15). Furthermore, increased basal expression of iHsp72 in monocyte-derived macrophages reduces the production of TNF-α and IL-1β in response to *in-vitro* LPS stimulation (36). This finding indicates an anti-inflammatory function of iHsp72 in this cell type.

Hsp72 is also released into the circulation, where its function differs from Hsp72 present within the cell. The tissues that excrete Hsp72 are not fully identified, but there is evidence that the liver, the brain and leukocytes release Hsp72 into the circulation through passive - as well as active - mechanisms (75). In a study using exercise as a stressor, Febbraio et al. (42) showed that skeletal muscle does not contribute to circulating eHsp72 concentrations. In contrast to the anti-inflammatory actions of iHsp72, extracellular Hsp72 (eHsp72) can activate monocytes through the TLR4/CD14 complex, inducing the production of pro-inflammatory cytokines (6). Indeed, elevated basal levels of eHsp72 are linked to impaired insulin sensitivity (28, 35, 85) and the development of atherosclerosis in individuals with hypertension (119). In further support of its potential role in chronic low-grade inflammation, resting eHsp72 concentrations strongly correlate with resting serum TNF-α and CRP concentrations in elderly individuals (111). Thus, by stimulating the production of pro-inflammatory cytokines in circulating immune cells, eHsp72 may exacerbate chronic low-grade inflammation and exert a negative effect on health. As the extracellular, pro-inflammatory, function of Hsp72 appears to differ from the cytoprotective function when present in the cell, it has been suggested that the ratio between extra- and intracellular Hsp72 expression could be a determinant for insulin resistance and T2DM risk (86).

Despite the cross-sectional data suggesting a negative role of eHsp72 on several aspects of health, evidence for its potential to induce pro-inflammatory cytokine release in monocytes and other leukocytes is equivocal (75). It has been suggested that the activation of monocytes following *in-vitro* incubation with eHsp72 can be the consequence of contamination with endotoxins, as opposed to the effect of eHsp72 itself (14, 49). For example, incubating monocyte-derived dendritic cells with endotoxin-free Hsp70 does not induce an acute inflammatory response (14). Moreover, pre-incubation of eHsp72 with polymyxin-B to block the actions of the contaminant LPS abolishes the production of pro-inflammatory cytokines in macrophages (49). Therefore, future *in-vitro* research on the mechanistic actions of eHsp72 should carefully control for possible contamination by endotoxins.

The anti-inflammatory effects of exercise – and the role of temperature

The following evidence derived from the exercise literature helps to understand and partly informs the inflammatory response to hyperthermia. It is heavily summarised; for a broader view on exercise and inflammation, the reader is directed to previous excellent reviews, for example by Gleeson et al. (54) and Petersen and Pedersen (118).

1. **Acute exercise**
   If of sufficient intensity and duration, a bout of exercise induces an acute inflammatory and subsequent anti-inflammatory response, which is thought to be partly responsible for the protective effects of regular exercise (54, 118). IL-6 responds most dramatically to acute exercise and has been suggested to be a main driver of the anti-inflammatory effects of exercise, because the acute post-exercise peak of IL-6 is followed by elevated anti-inflammatory cytokine concentrations (118). Indeed, infusion of recombinant human IL-6 in healthy humans at rest shows that IL-6 independently triggers the production of anti-inflammatory cytokines such as IL-1ra or IL-10, and it increases plasma concentrations of cortisol, a hormone with anti-inflammatory properties (132). Furthermore, acute exercise can increase iHsp72 (108,

112) and eHsp72 concentrations (148), while suppressing TNF-α and IL-1 production (117). The distribution of monocyte subsets within the peripheral circulation is also affected by acute exercise. Most studies report an acute increase in intermediate and non-classical monocytes directly following the cessation of exercise (33, 69, 136), but increases in classical monocytes following exercise have also been reported (94, 103). Potentially reflecting the change in circulating monocyte subsets, reduced monocyte TLR expression in the two-hour recovery period following exercise has been reported (89), which may help explain the mechanisms behind the altered inflammatory profile following acute exercise.

The inflammatory response to exercise is affected by both exercise duration and intensity (117). Importantly, in the context of this review, the increase in body temperature contributes to this relationship. Exercise in the heat results in a greater inflammatory response when compared with exercise in thermoneutral or cold conditions (44, 51, 88, 122, 131). Moreover, clamping core temperature (T_{core}) by cycling in cold water can abolish the acute IL-6 response (122). The amplified acute cytokine response following exercise in the heat may be partly mediated by the increased plasma catecholamine concentrations (122) and carbohydrate utilisation when compared with exercise in thermoneutral or cold conditions (45).

2. **Regular exercise**

Regular exercise is protective against the development of T2DM and CVD (95, 126). Cross-sectional and longitudinal evidence suggests that regular physical activity can reduce chronic low-grade inflammation, as indicated by lower basal circulating concentrations of the inflammatory risk factors IL-6, eHsp72, and numbers of intermediate and non-classical monocytes (16, 54, 59, 152). Possible candidates to explain improvements in the inflammatory profile after exercise training are reductions in visceral adipose tissue (producing pro-inflammatory cytokines at rest) (40), reduced TLR expression on immune cells (47) and changes in the number and phenotype of circulating cells and immune cells residing in tissue (139).

3. **Heat acclimation studies**

Heat acclimation studies provide some insight on the inflammatory effect of exercise training in the heat (reviewed by Amorim et al. (4)). Basal iHsp72 expression has been particularly studied as a mediator for the enhanced heat tolerance after heat acclimation (87): Whereas three days of heat acclimation do not increase basal iHsp72 expression in peripheral blood mononuclear cells (99), ten days of heat acclimation seem sufficient to increase basal iHsp72 expression in peripheral blood mononuclear cells (3, 105). Furthermore, the link between iHsp72 and markers of metabolic health, such as insulin sensitivity (63), suggests that heat acclimation-type exercise training may have wider-reaching effects than on exercise performance alone.

Who benefits from passive heating interventions?

Over the past decade there has been an alarming increase in number of people suffering from T2DM and CVD in the general population (150). The prevalence of these diseases is even higher in those with obesity (12), the elderly (31), or individuals with a physical disability, such as spinal cord injury (SCI) (13). Given the anti-inflammatory benefits of exercise outlined briefly above, it is unsurprising that a common trait of these populations is a reduced physical capacity. Despite this, there is still promise for exercise interventions. Even low-intensity exercise interventions such as regular walking can induce improvements in inflammatory markers in at-risk populations (142). For populations restricted to upper-body exercise modalities (e.g., wheelchair users) it is worth noting that this can induce an acute inflammatory response despite the smaller active muscle mass when compared with lower body exercise (67). Indeed, comparable inflammatory responses have been reported between upper and lower body exercise matched for relative intensity (94). Further, cross-sectional evidence (107), as well as some (10, 124) - but not all (140) - longitudinal upper-body exercise interventions indicate that upper body exercise can reduce inflammatory risk markers in SCI. Metabolic markers such as fasting glucose and insulin in people with SCI are also positively affected by physical activity (23).

Because reductions in physical *capacity* per se do not preclude the inflammatory effects of exercise, it is conceivable that the below-average physical *activity* levels in these at-risk populations (100, 137) contribute to their elevated disease risk. Indeed, environmental, social, and physical barriers to exercise have been identified (97, 143), which may go some way to explain the increased risk for chronic disease. Furthermore, for some populations, exercise of adequate intensity and duration may not be feasible or tolerable. These populations include those with acute injuries (e.g., musculoskeletal injuries, patients recovering from surgery), movement restrictions (e.g., due to obesity, spasticity), secondary complications to chronic disease (e.g., diabetic foot for T2DM, pressure sores for conditions leading to immobility), or cognitive impairments (e.g., dementia). An alternative or addition to exercise may hence represent a welcome strategy for these individuals. Because the acute inflammatory response to exercise is partly mediated by the rise in body temperature (88, 149), it is conceivable that passive heating strategies have the potential to improve the inflammatory profile. Similar to exercise, these strategies have the benefit of being low-cost, non-pharmacological interventions, reducing the financial strain on health-care providers.

The acute inflammatory response to passive heating

There are several ways to increase body temperature passively in humans, of which sauna bathing and hot water immersion (HWI) are the most commonly used. These methods are associated with a range of positive health outcomes, such as weight loss (70), improved sleep quality (37) and vascular

function (21, 27). Nevertheless, the potential of passive heating to reduce chronic low-grade inflammation and improve metabolic health has received relatively scarce attention.

Cytokines

It is suggested that contracting muscle is responsible for the increased circulating concentrations of IL-6 following exercise (134). Animal studies show that the IL-6 production in skeletal muscle increases following passive heat stress as well (146). Welc et al. (145) demonstrated that the upregulation of IL-6 production may be the consequence of HSF-1 activation. Another suggested mechanism for IL-6 release from the muscle in response to hyperthermia is through increased calcium influx after activation of the thermosensitive transient receptor potential 1 (113). Although these studies have provided rationale to study passively elevating body temperature in the context of chronic low-grade inflammation, it should be noted that in animal studies T_{core} is increased to a much larger extent than considered safe in human participants (50, 127, 146). This could make passive heating interventions less potent inducers of an acute inflammatory response in humans. For example, Gupte et al. (57) kept the T_{core} of mice between 41.0° and 41.5°, while in human studies the maximal attained T_{core} during HWI remained between 38° and 39° (41, 66, 114). Furthermore, due to the difference in size between species - and concomitant higher inertia in T_{core} during passive heating in larger species - T_{core} of humans takes considerably longer than that of small animals to increase to a given threshold. This is another important difference between human and animal research to date, in addition to the often reported higher T_{core} investigated in animals.

An overview of studies investigating the acute response of inflammatory markers following passive heating is provided in Table 1. Despite smaller increases in T_{core} during passive heating in human compared with animal studies, 1−2 h HWI induces an acute circulating IL-6 response in humans (41, 66, 88, 93). Consistent with exercise studies (46), this acute IL-6 response appears to be dose-dependent. Laing et al. (88) reported a ~12 fold increase in IL-6 immediately following 2 h HWI in water set at 38.5° while 1 h HWI only results in a ~2−3 fold increase in plasma IL-6 concentration (41, 66, 93).

Heat shock protein

The activation of HSF-1 by passive heating not only results in increased IL-6, but also increased iHsp72 production (146). Raising the temperature of human blood ex-vivo indeed results in an acute increase in iHsp72 expression (68), which is consistent with findings in animal passive heating studies (57, 79). In Vervet monkeys, maintaining T_{core} between 39° and 41° for 30 min using HWI results in a significant increase in *hsp72* expression in skeletal muscle. In addition, maintaining T_{core} of rats around 41.0−41.5° for 20 min using a thermal blanket leads to a ~three-fold increase in iHsp72 protein

Table 1. The acute effect of passive heating on inflammatory markers in humans.

Reference	Design	Population	Main outcomes
Brunt et al., 2018 (22)	1 h HWI up to the shoulder in water set at 40.5°C	Healthy inactive men (N=6) and women (N=4) and sex-matched controls (N=10)	Serum concentration eHsp72 ↔, IL-6 ↑; peripheral blood mononuclear cell iHsp72 ↑
Faulkner et al., 2017 (41)	1 h HWI up to the waist in water set at 40°C	Healthy men (N=14)	Plasma concentration eHsp72 ↑, IL-6 ↑
Hafen et al., 2018 (58)	2 h heating of skeletal muscle using pulsed wave diathermy	Healthy sedentary men (N=10) and women (N=10)	Skeletal muscle iHsp72 ↔
Hashisaki et al., 2018 (60)	1 h in water-perfused suit to achieve 1°C rise in T_{core}	Individuals with spinal cord injury (N=19) and able-bodied controls (N=8)	Serum concentration IL-6 ↑, TNF-α ↔
Hoekstra et al., 2018 (66)	1 h HWI up to the neck in water set at 39°C	Healthy overweight sedentary men (BMI = 31±4 kg/m^2; N=10)	Plasma concentration eHsp72 ↔, IL-6 ↑; monocyte iHsp72 ↔
Iguchi et al., 2012 (74)	30 min in room set at 73°C	Healthy men (N=13) and women (N=12)	Plasma concentration eHsp72 ↑
Laing et al., 2008 (88)	2 h HWI in water set at 38.5°C	Healthy men (N=13)	Serum concentration IL-6 ↑
Leicht et al., 2015 (93)	1 h HWI up to the neck in water set 2°C higher than resting T_{core}	Men with spinal cord injury (N=7) and able-bodied controls (N=8)	Plasma concentration IL-6 ↑, IL-1ra ↑, TNF-α ↔
Morton et al., 2007 (109)	1 h HWI of one leg in water set at 45°C	Healthy men (N=7)	Skeletal muscle iHsp72 ↔
Oehler et al., 2001 (114)	2 h HWI up to the neck in water set at 39.5°C	Healthy men (N=6) and women (N=6)	Monocyte iHsp72 ↑
Whitham et al., 2007 (149)	2 h HWI in water set at 38.5°C; control at 35°C	Healthy men (N=11)	Plasma concentration eHsp72 ↔
Zychowska et al., 2017 (156)	30 min sauna bathing at 98°C	Healthy men (N=18)	leukocytes: *hsp72* mRNA expression ↔, IL-6 ↔, IL-10 ↔

Abbreviations: eHsp72, extracellular heat shock protein 72; HWI, hot water immersion; iHsp72, intracellular heat shock protein 72; IL, interleukin; IL-1ra, interleukin-1 receptor antagonist; mRNA, messenger ribonucleic acid

expression in skeletal muscle when compared with control (57). Of note, the acutely increased iHsp72 expression in these two studies was also associated with improved insulin sensitivity.

Despite promising evidence from animal and isolated tissue studies, the iHsp72 response in human whole-body models shows mixed results. Some of the variation may be confounded by the tissue analysed, with relatively few studies investigating skeletal muscle iHsp72 following passive heat stress. This lack of studies may be related to the invasive nature of skeletal muscle sampling. Harvesting monocytes by venepuncture is relatively easy in comparison, and some of the human evidence on passive heating is therefore based on monocyte iHsp72 (66, 114), due to monocyte responsiveness to heat stress (8). Although the acute iHsp72 response to exercise in total leukocytes is similar to the response in skeletal muscle (141), comparing results from studies investigating different cell/tissue types must be done with due caution.

To date, only four studies have investigated the acute iHsp72 response to HWI in humans. These studies found no increase in skeletal muscle (109) or monocytes (66) after 1 h, but an increase in PBMC iHsp72 after 1h (22), and an increase in monocyte iHsp72 expression after 2 h HWI (114). Time is a likely determinant of the iHsp72 response. This is supported by Gibson et al. (52), who demonstrated that T_{core} needs to be maintained above 38.5° for at least 27 min to induce the upregulation of *hsp72* expression following exercise. The extent to which T_{core} is elevated is a likely additional explanatory factor. T_{core} increased by approximately 1.7−2.0ºC in the study showing increases in monocyte iHsp72 expression (22, 114), whereas the increase was ~1.5ºC in the studies showing no change in this parameter (66, 109).

There are limited data about the potential of HWI to induce an acute increase in eHsp72 concentration in humans. Faulkner et al. (41) reported a similar increase in eHsp72 concentration following HWI when compared with exercise matched for heat production. The elevation of muscle temperature was the strongest predictor for the eHsp72 response, explaining 27% of its variance (41). Passive heating by 30 min of sauna bathing, resulting in a 0.8° T_{core} increase, also leads to the elevation of eHsp72 concentrations (74). In contrast, Brunt et al. (22), Hoekstra et al. (66) and Whitham et al. (149) found no significant acute change in eHsp72 following HWI in water set at 38.5−40.5°. Therefore, partly due to the lack of a control condition in some studies and the different designs across studies, the potential of passive heating to elevate eHsp72 concentrations remains equivocal.

Chronic adaptations to passive heating interventions

Acute studies have confirmed the potential of HWI to induce an inflammatory response (41, 66, 88, 93, 114), which has led to the suggestion that chronic HWI treatment may help to reduce chronic low-grade inflammation and improve metabolic health (71, 86, 104, 138). Although there are currently limited human data to support this notion, animal studies provide some insight into the efficacy of chronic passive heat therapy and the few human studies available show promise.

Most animal studies investigating the effect of chronic passive heat therapy on metabolic health and chronic low-grade inflammation have focussed on basal iHsp72 expression and its impact on insulin sensitivity (30, 56, 79, 127). In mice, heat therapy for 16 weeks increased basal iHsp72 expression in skeletal muscle concurrently with improved insulin sensitivity when compared with a sham control condition (30). To further support the importance of iHsp72 for insulin sensitivity, increasing iHsp72 expression by pharmacological means or genetic manipulation resulted in similar improvements in insulin sensitivity (30). A simultaneous increase in basal iHsp72 expression and improvement in insulin sensitivity was also reported in the studies by Gupte et al. (56) and Silverstein et al. (127). Mechanistically, the link between both adaptations following passive heating appears to involve the inhibition of JNK and NF-κB activation (63). Indeed, Chung et al. (30) and Gupte et al. (56) reported reduced activation of these pathways following passive heat therapy. Moreover, in humans, low iHsp72 expression is associated with impaired insulin sensitivity, but also elevated JNK activity (30) (Figure 1).

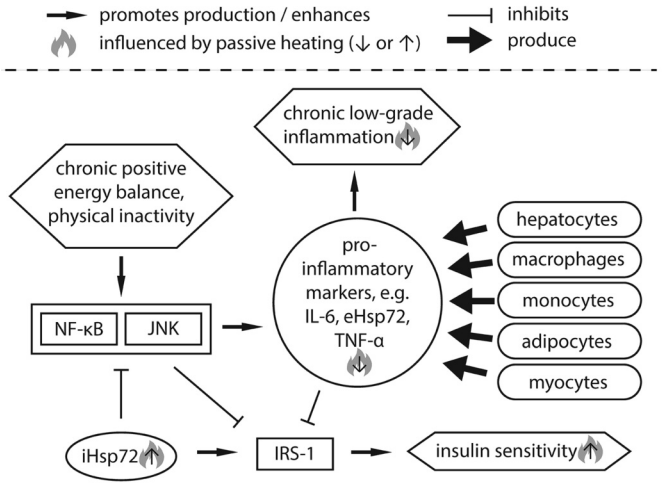

Figure 1 - Chronic impact of passive heating on markers related to inflammation and glycaemic control: overview of evidence to date. A chronic positive energy balance, eventually resulting in obesity, leads to the activation of NF-κB and JNK pathways. This results in an enhanced production of pro-inflammatory proteins and inhibits insulin receptor substrates, attenuating insulin sensitivity. Passive heating has the potential to counteract some of these negative adaptations, reducing inflammation and enhancing insulin sensitivity. eHsp72, extracellular heat shock protein 72; iHsp72, intracellular heat shock protein 72; IL-6, interleukin-6; IRS-1, insulin receptor substrate-1; JNK, c-Jun N-terminal kinase; NF-κB, nuclear factor kappa B; TNF-α, tumour necrosis factor α.

In a series of studies, Kavanagh et al. (28, 79, 80) showed that the increase in iHsp72 can also lead to beneficial adaptations in non-human primates, a species genetically closer to humans. In these animals, two HWI sessions per week for five weeks increased basal iHsp72 expression in skeletal muscle, which was strongly associated with fasting blood glucose and the insulin responses during an intravenous glucose tolerance test (79). In keeping with the data derived from mice (30),

pharmacological induction of iHsp72 expression also increased iHsp72 expression and improved insulin sensitivity in non-human primates (80). Together, animal studies have highlighted the potential for chronic passive heating interventions to improve the inflammatory profile and metabolic health, possibly through the elevation of basal iHsp72 expression.

Epidemiological studies indicate that sauna bathing can reduce systemic inflammation (90), as well as all-cause mortality (91). Epidemiological data further show that habitual hot-spa bathing is linked to a lower incidence of hypertension and CVD (98). These findings are supported by controlled passive heating interventions investigating resting inflammatory and metabolic markers in humans, as summarised in Table 2. Hooper (70) showed that three weeks of HWI reduces fasting glucose and glycated haemoglobin concentration in people with T2DM. A reduction in fasting glucose concentration was also observed following two weeks of sauna therapy in patients with congestive heart failure (18), or two weeks of HWI in overweight (but otherwise healthy) individuals (66). Moreover, a two-week HWI intervention reduces plasma IL-6 concentration at rest in people with chronic heart failure (115), and four weeks of sauna therapy reduces IL-6 mRNA expression in leukocytes (156). In contrast, no changes in resting plasma concentration of IL-6 were found in healthy individuals following two- (66) or eight-week (22) HWI interventions, or nine days of passive heat acclimation (77).

The lack of improvements in inflammatory markers following repeated passive heating reported in some of these studies may be linked to the populations that were under investigation, who do not always present with an increased risk for metabolic ill-health *prior* to the chronic intervention (66). For other investigations, the reason could also lie in the relatively modest body temperature increase that was induced in each session, or in the fact that the effect of the acclimation period was assessed on the day after the last passive heating session (77), possibly resulting in the assessment of acute instead of chronic effects. Despite these caveats, the existing evidence suggests that, providing

Table 2. The effect of chronic passive heating interventions on inflammatory and metabolic markers in humans.

Reference	Design	Population	Main outcomes
Brunt et al., 2018 (22)	8 weeks HWI with 36 sessions of 60 min in water set at 40.5°C	Healthy inactive men (N=6) and women (N=4) and sex-matched controls (N=10)	Serum concentration eHsp72 ↔, IL-6 ↔; peripheral blood mononuclear cell iHsp72 ↑
Biro et al., 2003 (18)	2 weeks of daily sauna bathing for 15 min at 60°C + blanket for 30 min	Healthy obese (BMI>30 kg/m^2; N=10)	Fasting glucose concentration ↓
Ely et al., 2019 (39)	8–10 weeks HWI with 30 sessions of 60 min in water set to maintain 38.5–39.0°C of core temperature	Obese women with polycystic ovary syndrome (BMI = 41±1 kg/m^2; N=9 intervention, N=9 resting control)	Fasting glucose concentration ↓, oral glucose tolerance test AUC ↓, adipose tissue insulin signalling ↑
Hafen et al., 2018 (58)	6 days of 2 h heating of skeletal muscle using pulsed wave diathermy	Healthy sedentary men (N=10) and women (N=10)	Skeletal muscle iHsp72 ↑
Hesketh et al., 2019 (64)	6 weeks of passive heating 40–50 min at room air of 40°C	Healthy sedentary (N=10 intervention, N=10 exercising control)	Oral glucose tolerance test AUC ↓
Hoekstra et al., 2018 (66)	2 weeks HWI with 10 sessions of 45–60 min in water set at 39°C	Healthy overweight sedentary men (BMI = 31±4 kg/m^2; N=10 intervention, N=8 resting control)	Fasting glucose ↓, plasma concentration eHsp72 ↓, IL-6 ↔; monocyte iHsp72 ↔,
Hooper, 1999 (70)	3 weeks HWI with 18 sessions of 30 min in water set between 37 and 41°C	Patients with Type 2 Diabetes Mellitus (N=8)	Fasting glucose ↓, glycosylated haemoglobin concentration ↓
Kanikowska et al., 2012 (77)	9 sessions of 10 min HWI in water set at 42°C + blanket for 90 min in 40°C room	Healthy men (N=6)	Plasma concentration IL-6 ↔, TNF-α ↔
Kihara et al., 2002 (83)	2 weeks of daily sauna bathing for 10 min at 60°C + blanket for 30 min	Patients with chronic heart failure (N=20)	TNF-α ↔
Masuda et al., 2004 (102)	2 weeks of daily sauna bathing for 10 min at 60°C + blanket for 30 min	Patients with at least one coronary risk factor (N=14 intervention, N=14 resting control)	Fasting glucose ↔
Oyama et al., 2013 (115)	2 weeks HWI with 14 sessions of 10 min in water set at 40°C	Patients with chronic heart failure (N=16 intervention, N=16 resting control)	Plasma concentration IL-6 ↓, CRP ↓, TNF-α ↓
Zychowska et al., 2018 (155)	4 weeks of sauna bathing, 12 sessions, for 30 min at 98°C	Healthy men (N=22)	Leukocyte: *hsp72* mRNA expression ↓, IL-6 ↓*, IL-10 ↑

Abbreviations: AUC, area under the curve; BMI, body mass index; CRP, C-reactive protein; eHsp72, extracellular heat shock protein 72; HWI, hot water immersion; iHsp72, intracellular heat shock protein 72; IL, interleukin; mRNA, messenger ribonucleic acid; TNF-α, tumour necrosis factor-α. *trend for a decreased resting IL-6 mRNA expression.

sufficient thermal load, improvements in markers for glucose metabolism and chronic low-grade inflammation can be achieved in as little as two weeks. Because animal studies that have induced elevations in basal iHsp72 expression have used longer duration protocols (30, 127), this leaves the question of whether the observed improvements in glucose metabolism reported in humans are orchestrated by the actions of iHsp72. Indeed, no changes in iHsp72 in the presence of fasting glucose reductions have been found following two weeks of HWI in humans (66). Furthermore, as human studies often report more moderate increases in T_{core} than animal studies, it is not uncommon that acutely, iHsp72 remains unaffected (Table 1). It is therefore debatable whether acute increases in iHsp72 are required for a passive heating intervention to be beneficial in context of inflammation and glycaemic control. Other markers of inflammation (e.g., IL-6) do show acute perturbations in the absence of changes in iHsp72, and chronic interventions can improve glycaemic control using protocols of a duration and moderate heat stress too short or not sufficiently intense to acutely increase iHsp72 expression (Table 2).

Future research

The presented evidence supports a potential therapeutic role of passive heating interventions to reduce chronic low-grade inflammation that may particularly benefit clinical populations. However, such interventions bring their own challenges. For example, some populations exhibit impairments of thermoregulatory capacity, including those with T2DM (26) and those with SCI (55). Notwithstanding this, even in populations with normal thermoregulatory control, sweating is largely ineffective for regulating body temperature during HWI interventions due to the inability to decrease body temperature through evaporative heat loss. These clinical populations may therefore not be at a disadvantage *during* HWI. However, impaired thermoregulation affects the return of body temperature to normal *following* HWI (93), which may increase the risk in any emergency situations where a quick return of body temperature is warranted. Furthermore, heat interventions during which skin is exposed to air may induce accelerated elevations of body temperature in these at-risk populations (55). Heat therapy may also be associated with a higher risk for adverse events in the elderly and people with hypertension, T2DM, cardiovascular disease, or allergies (86). Indeed, heart disease is the main natural cause of death during sauna bathing, heat being a contributing factor in half of cases, and the main cause in a quarter of the deaths investigated in one particular study (81). It is further yet to be determined whether the acute elevations in postprandial glucose concentrations following HWI (92) occur in people with T2DM, and whether this might hence influence the feasibility of HWI interventions in this population. Therefore, protocols that have not been adapted and developed for at-risk populations must be carefully evaluated in order to avoid heat illness related events.

Developing protocols that are tolerable and, ideally, enjoyable, should form an important part of future investigations. For example, it could be questioned whether a 120-min HWI session inducing a rise in T_{core} of 2.0ºC as studied by Oehler et al. (114) is realistic to implement in a practical setting, as even a 60-min HWI session inducing a rise in T_{core} of 1.6ºC can be perceived as uncomfortable (66) and physiologically straining (123). Therefore, protocols that induce minimal heat stress stimuli associated with improvements in health markers need to be identified. This may hence improve subjective perceptions of passive heating interventions. Similar to the approach taken in the development of exercise guidelines in a clinical population (SCI) (101), a focus might be put on finding minimal, rather than optimal, heat-doses to induce health benefits. Subjective perceptions may also be improved by targeting specific parts of the body rather than taking a whole-body approach; for example, local heating might reduce whole body heat strain. Such an approach can still result in noteworthy metabolic changes, as shown for targeted heating of one leg, resulting in increased glucose uptake when compared with the contralateral control leg (29). Alternatively, localised cooling might make whole-body heating protocols more tolerable. Finally, different populations (e.g., male/female, young/old, healthy/clinical) may present different characteristics regarding thermoregulation, heat perception and inflammatory profiles. Therefore, specific populations need investigating in detail, because the majority of evidence in controlled human laboratory studies is derived from young, healthy males.

Conclusions

Chronic low-grade inflammation is increasingly recognised in the aetiology of chronic diseases, such as T2DM and CVD. Although exercise can effectively reduce chronic low-grade inflammation, it may not be a feasible intervention to adhere to regularly for populations with reduced physical capacity and/or barriers to exercise. Because the increase in body temperature partly mediates the exercise-induced acute inflammatory response, passive heating strategies may have potential as an alternative or addition to exercise to reduce chronic low-grade inflammation. Indeed, the passive elevation of body temperature acutely influences a range of inflammatory markers that are affected by exercise, which is supported by human, animal and cell culture studies. A small but growing number of chronic passive heating interventions in humans have further explored its effect on inflammatory and metabolic markers. Whereas the literature on improvements of glycaemic control after repeated passive heating in humans is relatively convincing, consistent evidence for improvements of the inflammatory profile has so far been limited to animal studies. This limitation may be related to the reduced thermal load and the relatively short-duration chronic interventions that were investigated in humans. The development of effective and tolerable passive heating protocols to improve the inflammatory profile, alongside glycaemic control, using longer-term chronic interventions in humans should therefore be the aim of further investigations.

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