# Heat shock proteins and heat therapy for type 2 diabetes: pros and cons

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**Purpose of review**
Heat therapy, such as sauna and hot tub, has become an increasingly regular therapeutical practice around the world since several studies have shown benefits of heat therapy in metabolic and cardiovascular diseases. The use of heat therapy in people with type 2 diabetes mellitus revealed a striking reduction of 1% unit in the glycated hemoglobin, suggesting this therapy for the treatment of diabetes. Herein, we shall discuss the use of heat therapy and the mechanisms involved, and suggest a provisional guide for the use of heat therapy in obesity and diabetes.

**Recent findings**
Human studies indicate that heat therapy reduces fasting glycemia, glycated hemoglobin, body weight, and adiposity. Animal studies have indicated that nitric oxide and the increase in heat shock protein 70 expression is involved in the improvements induced by heat therapy on insulin sensitivity, adiposity, inflammation, and vasomotricity.

**Summary**
Heat therapy is a promising and inexpensive tool for the treatment of obesity and diabetes. We proposed that transient increments in nitric oxide and heat shock protein 70 levels may explain the benefits of heat therapy. We suggest that heat therapy (sauna: 80–100°C; hot tub: at 40°C) for 15 min, three times a week, for 3 months, is a safe method to test its efficiency.

**Keywords**
heat shock protein 70, heat therapy, inflammation, nitric oxide, type 2 diabetes mellitus

## INTRODUCTION

Heat therapy, such as sauna and hot tubs, is a very common practice in Scandinavia and the Middle East countries where it is believed to have a therapeutic purpose [1]. The use of heat therapy has become an increasingly regular practice around the world since several studies have shown the benefits of heat therapy for people with metabolic and cardiovascular diseases [1,2]. Although considered safe for most people, some reports have indicated that heat therapy may represent risks for health in certain conditions (e.g. cardiovascular diseases) and populations (e.g. elderly) [3].

The use of heat therapy in metabolic diseases has brought attention after the observation that sauna, in insulin-dependent diabetic men, caused hypoglycemia symptoms. However, the most provocative finding of the use of heat therapy in metabolic disease was demonstrated by Hooper [2]. In this study, patients with type 2 diabetes mellitus (T2DM) were submitted to hot tub sessions for 3 weeks. The patients' oral temperature raised only by an average of 0.8°C each session, but the main outcome was a significant reduction in plasma glucose and glycated hemoglobin ($HbA_{1c}$) levels [2]. The striking reduction of 1% unit in $HbA_{1c}$ [from $11.3 \pm 3.1$ percentage to $10.3 \pm 2.6$ percentage ($P = 0.004$)] in a short-term intervention suggested

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## KEY POINTS

- Heat therapy is a promising tool for the prevention and treatment of obesity and diabetes.
- Heat therapy has been shown to reduce inflammation, body fat deposition, insulin resistance, body weight, and cardiovascular diseases.
- The mechanism(s) involved in heat therapy-elicited improvements, appear(s) to be connected to the increments on body temperature and the chronic transient-elevations of nitric oxide, initiating a cycle that will induce HSP70 expression. As the heat therapy continues, the elevated levels of HSP70 (arising from the previous heat therapy sessions) will enhance the phosphorylation of AKT, AMPK, and eNOS. Together, higher (or normalized) nitric oxide levels, HSP70, AMPK, and eNOS will improve insulin signaling, body composition, endothelial dysfunction, and the low-grade inflammation found in people with diabetes.
- Heat therapy, respecting the contraindications, can be safely used with sedentary (or unable to perform exercise) obese and diabetic people.
- Heat therapy (sauna: 80–100°C; hot tub: at 40°C/15 min), three times per week for 3 months, is a safe method to be used in this population and to test the efficiency of this therapy.

that heat therapy could be useful for T2DM treatment. Remarkably, 16 years after the first trial, only two additional interventions using heat therapy in obese and T2DM patients were conducted [4,5]. In the first one, quality of life was evaluated, and in the second, the results of a sauna treatment for obese people, which claimed to reduce body weight and fat, were described [5].

Because of the reduced number of studies in humans regarding heat therapy, and their limitations, the mechanisms of how heat therapy induces benefits for obese and diabetic people remain unknown. On the contrary, several studies were conducted using heat therapy in animals and in-vitro models [6▪▪,7▪▪,8▪]. The improvements in insulin sensitivity found were attributed, in part, to the expression of the 70-kDa heat shock protein (HSP)70, whose intracellular expression in skeletal muscle was found to be decreased in obesity and diabetes [9] and was highly induced by heat therapy [7▪▪]. Reduced HSP70 expression is a common feature in several conditions associated with low-grade inflammation such as T2DM, aging, and obesity [8▪,9,10▪▪]. Therefore, strategies to restore heat shock response (the biochemical pathway leading to inducible HSP synthesis) may amend the metabolic defects associated with inflammation. In this study, we shall discuss the efficiency, safety, and mechanisms involved in heat therapy as a promising treatment for people with obesity and diabetes. Additionally, we aimed to suggest a provisional guideline for the use of heat therapy within this population.

## CHRONIC INFLAMMATION IN OBESITY AND DIABETES IS A TARGET FOR HEAT THERAPY

Obesity is often associated with a vicious cycle in which adipose tissue expansion increases the levels of free fatty acids and proinflammatory cytokines in circulation, which, conversely, increase the synthesis and accumulation of intramyocellular triglycerides (IMCT) [11]. Sedentary behavior is related to a decreased mobilization of IMCTs resulting in an increased synthesis of toxic fatty acid-delivered metabolites, causing an elevation in the production of reactive oxygen species (ROS), nitrogen reactive species (RNS), resulting in oxidative stress, mitochondrial dysfunction, and the activation of stress associated transcription factors such as nuclear transcription factor κB (NF-κB), followed by the increased production and release of proinflammatory cytokines [11]. Among them, tumor necrosis factor-α (TNF-α) has been shown to activate serine threonine kinases, such as c-Jun $NH_2$-terminal kinases (JNKs) and inhibitor of κB kinases (IKK) [6▪▪,7▪▪,8▪] that can phosphorylate insulin receptor substrate-1 (IRS-1) on serine (Ser-307) instead of at tyrosines, leading to the inactivation of the insulin signaling cascade [6▪▪,7▪▪,8▪]. Excessive levels of ROS/RNS not only directly damage cells by oxidizing DNA, protein, and lipids, but indirectly they also damage cells through the activation of a variety of stress-sensitive/inflammatory intracellular signaling pathways such as NF-κB, p38-mitogen-activated protein kinase, JNK/stress-activated protein kinase, hexosamine, and others [12]. Since chronic inflammation negatively affects insulin sensitivity, the control of key inflammatory transcriptional factors, such as the NF-κB, is critical for the maintenance of insulin signaling [11]. It has been shown that heat therapy is effective to reduce the activation of NF-κB and other inflammatory mediators, thus improving insulin signaling in animal models [6▪▪,7▪▪,8▪].

## 'PROS', MECHANISMS, AND THE ROLE OF THE NITRIC OXIDE-HSP70 CYCLE ON THE HEAT THERAPY BENEFITS

Heat shock proteins are considered part of a family of proteins known as 'stress proteins' since their expression is induced by a wide range of stressors

[6▪▪]. The functions attributed to HSP70 include its action as a molecular chaperone, in protein translocation, antiapoptosis, and anti-inflammatory responses [6▪▪,7▪▪]. It has been reported that HSP70 mRNA and protein levels [9] are decreased in skeletal muscle of T2DM patients, which is correlated with insulin resistance [6▪▪], whereas heat therapy and heat shock-like therapies (i.e. whole body warming, HSP transgenic overexpression, or pharmacological co-inducers of HSP70 protein expression) protect against high-fat diet (HFD) and obesity-induced hyperglycemia, hyperinsulinemia, glucose intolerance, and insulin resistance in animal models [6▪▪,7▪▪,8▪]. The anti-inflammatory effect of HSP70 is attributed mainly to its capacity of interaction with NF-κB, decreasing its activity [13]. HSP70 is able to associate with the complex formed by NF-κB with its inhibitor (IκB), stabilizing this complex and thus impeding NF-κB translocation to the nucleus [13]. HFD and/or high carbohydrate intake may result in increased oxidative stress and consequent NF-κB activation in obese individuals [11]. On the contrary, NF-κB DNA-binding is suppressed after heat shock [14], and up-regulation of HSP72 (an inducible HSP70 form) can negatively affect NF-κB activity in skeletal muscle [14].

Heat therapy is capable of inducing HSP72 expression in several tissues, preventing various obesity-elicited metabolic effects at molecular level, improving glucose tolerance, insulin-stimulated glucose transport, and insulin signaling, accompanied by the reduction in JNK and IKKβ activities [6▪▪,7▪▪,8▪] on HFD-fed mice, which is almost completely abolished in transgenic $HSP72^{+/+}$ mice [6▪▪,7▪▪,8▪]. Enhanced activation rate of JNK phosphorylation is associated with glucose intolerance and insulin resistance in skeletal muscle of obese mice, an effect which may be attenuated by long-term heat therapy (16 weeks, 41.5 °C) and is also observed in transgenic $HSP72^{+/+}$ mice [6▪▪,7▪▪,8▪]. Finally, studies have demonstrated that HSP70 is able to bind to the insulin receptor, enhancing its recycling rate after heat shock [6▪▪], which suggests that HSPs may have direct influence upon insulin receptor function and activity.

The evidence that heat therapy improves obesity and diabetes is wide; however, the majority of studies are regarded to animal and in-vitro studies. Therefore, will heat therapy result in the same outcome in humans? Are the mechanisms the same? When compared, the protocols of heat therapy in animals and humans, there is a major difference – body temperature. Whereas in animal models of heat therapy, body temperature is raised from basal (∼36.5°C) up to 41/42°C, which is a significant approximate 5°C increase, in human studies, this is increased up to a maximum of 1.2°C. Is this increase in temperature enough to cause a significant increase in HSP70 expression in humans? There is no concrete evidence showing that HSP70 increases in humans with a passive increase in body temperature of only 1°C. Thus, the effects of heat therapy may be induced, at least initially, by changes in a more sensitive mechanism that might be activated immediately during temperature elevations, helping the body to exchange heat appropriately.

As previously demonstrated [15], whereas HFD-fed rats showed attenuated eNOS phosphorylation, 5′AMP-activated protein kinase (AMPK) phosphorylation, and sirtuin-1 (SIRT1) expression (thus deregulating nitric oxide production and vasodilation), heat therapy (41°C for 20 min/12 weeks) prevented the attenuation of these signaling pathways. In addition, inhibition of eNOS and SIRT1 prevented the benefits of heat therapy. The above findings suggest that induction of HSP70 by heat therapy enhances, at last, phosphorylation of AKT, AMPK, and eNOS expression in insulin-resistance states. As a result, more nitric oxide is produced, improving vasomotricity and vasoprotection. It is a reasonable thought indeed, however, when we observe the acute effects of heat therapy in humans (keeping in mind that core temperature does not elevate as in animal models), the most important effects observed are the changes in blood flow (↑skin, ↓ internal organs and skeletal muscle) and on the cardiac output (↑) related to vasodilatation for heat dissipation [16]. Differently from animals in which the anesthetic limited their capacity to control body temperature [17], all the homeostatic mechanisms for this control are still present and activated in humans. The mechanisms of temperature regulation were extensively studied and revised [16]; however, nitric oxide appears as a key modulator of blood vessel vasodilation during skin and internal heating.

Sympathetic nerve activity, which is involved in mediating cardiovascular and thermoregulatory responses, is increased in the skin and skeletal muscle during moderate passive whole body heating (increased internal temperature ∼0.7°C) [18], and there is now very strong evidence that the nitric oxide system is involved in vasodilation [16,18]. Nitric oxide synthase (NOS) inhibition showed such inhibition to limit the reflex vasodilator response to body heating [16,18]. Administration of nonspecific NOS inhibitors via microdialysis [16,18] or via brachial artery infusion [16,18] limited the reflex vasodilator response to body heating. As the cardiovascular effects of sauna and hot tub initiates rapidly after the initial skin heating [19], the increments in nitric oxide during the heat

therapy session may initiate the adaptations to the increased temperature. Therefore, we suggested a mechanism that may be involved in the benefits of heat therapy in humans, which includes increments in nitric oxide metabolism prior to the HSP70 expression (Fig. 1).

The role of nitric oxide in the synthesis of HSP70 has been previously demonstrated [20].

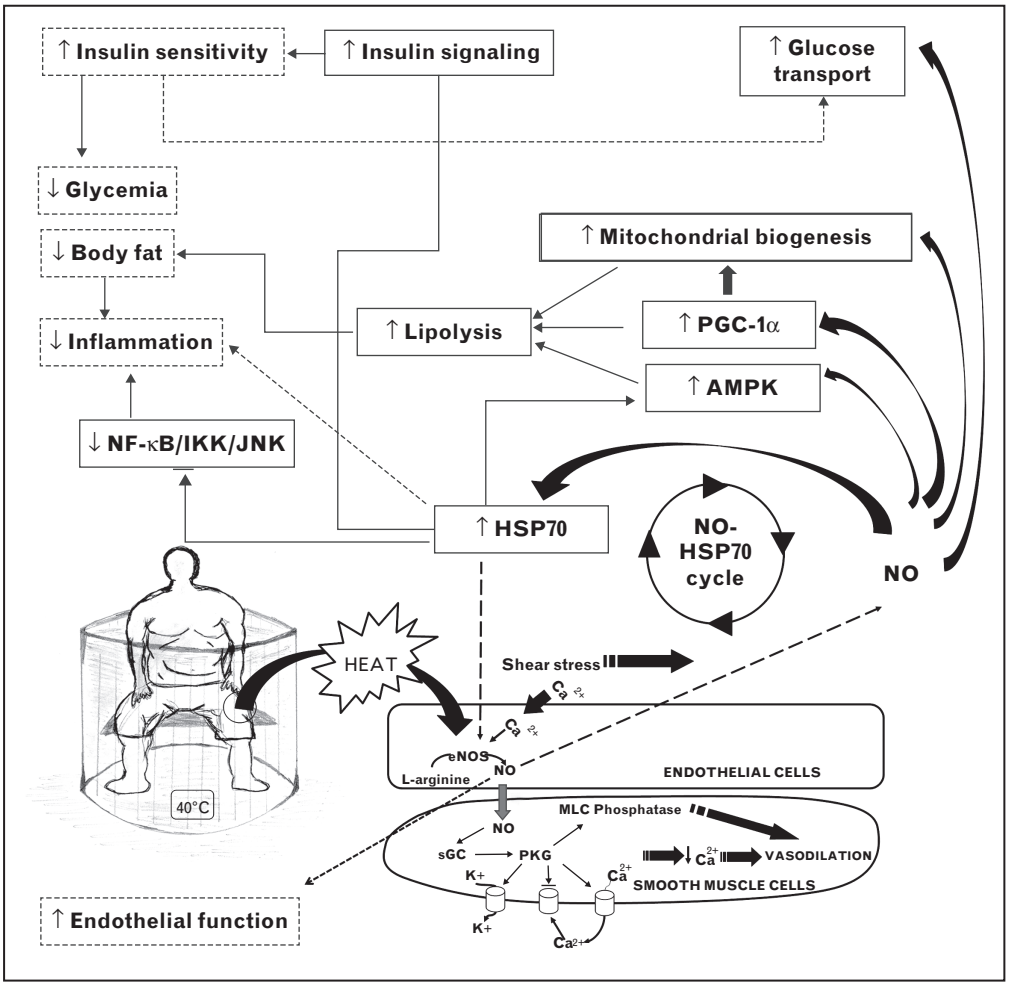


**FIGURE 1.** Heat therapy (HT) and the NO-HSP70 cycle. In humans, HT induces rapid changes in blood flow (↑) related to vasodilatation necessary for heat dissipation. NO is a key modulator of blood vessel vasodilation during skin and internal heating. HT produces great increased blood flow in the heated surface tissues of the body that leads to increased shear stress in the surface tissue vasculature, which induces NO production and release. Moreover, NO is an essential modulator of glucose uptake, participates in the activation of several enzymes related to oxidative metabolism and, of course, to vasomotricity. It has been shown that this increment in blood flow induces a coordinated up-regulation of arterial eNOS and the biosynthesis of tetrahydrobiopterin (BH4), a cofactor for all three nitric oxide synthases. Thus, as the cardiovascular effects of sauna and hot tub initiate rapidly after the initial skin heating, the increments in NO during the HT session may initiate the adaptations of the patient to the increased temperature. The chronic transient elevations of NO will initiate a cycle that will induce more HSP70 expression (NO-HSP70 cycle). As the HT continues, the elevated levels of HSP70 (arising from the previous session) will enhance, at last, phosphorylation of p-AKT, p-AMPK, and p-eNOS. As a result, more NO is produced, improving vasomotricity and vasoprotection under insulin resistance and diabetes. Increments in AMPK and peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) (that increases mitochondrial biogenesis) will also help to explain the finding on energy expenditure, body fat, and body weight decreases found after HT. The elevation of the HSP70 levels will lead to the inhibition/reduction of the inflammatory signaling from molecules such as the NF-κB, IKK, and JNK, all decreased by HT. The reduction of adiposity will also lead to a reduction on the low-grade inflammation. Together, higher (or normalized) NO levels, HSP70, AMPK, and eNOS would improve insulin signaling/sensitivity, body composition/body fat, endothelial dysfunction, and the low-grade inflammation found in people with diabetes. eNOS, endothelial nitric oxide synthase; HSP, heat shock protein; IKK, inhibitor of κB kinase; JNK, c-Jun $NH_2$-terminal kinase; NF-κB, nuclear transcription factor κB; NO, nitric oxide.

Accordingly, it has been shown that the NOS inhibitor nitro-L-arginine decreased HSP70 synthesis induced by heat therapy, suggesting that nitric oxide is involved in such induction. The antihypotensive effect of the adaptation to heat clearly demonstrates the cross-talk between nitric oxide and HSP70 [20]. Thus, we believe that the increments in body temperature and the chronic transient elevations of nitric oxide will initiate a cycle that will induce HSP70 expression. As the heat therapy continues, the elevated levels of HSP70 (arising from the previous heat therapy session) will enhance, at last, eNOS. As a result, more nitric oxide is produced, improving vasomotricity and vasoprotection under insulin resistance. In addition, it has been shown that this increment in blood flow induces a coordinated up-regulation of eNOS and the biosynthesis of tetrahydrobiopterin (BH4), a cofactor for all three nitric oxide synthases [11]. Together, higher (or normalized) nitric oxide levels (which is lower in people with diabetes [21] and have important metabolic and cardiovascular implications [12]), HSP70, AMPK, and eNOS would improve insulin signaling, body composition, endothelial dysfunction, and the low-grade inflammation found in T2DM patients (Fig. 1). In addition, heat therapy may induce the expression of the heat shock transcription factor-1 (HSF-1), which is the major responsible factor for the inducible expression of HSP70, through the activation of the $NAD^+$-dependent protein deacetylase of class III family SIRT1 [13].

Although increments in intracellular HSP70 may be beneficial for insulin signaling and inflammation, chronic elevation in the extracellular HSP70 (eHSP70) is associated with insulin resistance and pancreatic β-cell dysfunction/death [10▪▪]. Increments in body temperature may result in acute accumulation of eHSP70. Differently from chronic elevations, acute exposure may have differential effects. Similarly to moderate physical exercise, which is a known inducer of eHSP70 release, heat therapy may induce additional benefits by stimulating the activation of Akt (a downstream protein in the insulin-signaling cascade) through eHSP70 signaling, improving insulin signaling and normal intracellular HSP70 (iHSP70) expression [10▪▪]. In addition, acute elevation in eHSP70 may reduce whole-body sensitivity to Toll-like receptors 2 and 4 (TLR2/4), a known inducer of inflammation and insulin resistance [22▪▪]. The accumulative effects of heat therapy on eHSP70 levels remain to be determined.

## 'CONS' FOR THE USE OF HEAT THERAPY IN DIABETES

Although considered safe, some studies have raised concerns about the use of heat therapy [3,23–30]. The worries vary from allergy problems [23,24], risk of miscarriage [25], ketoacidosis [1], physical injuries, and death risks [3]. The findings on the risks involving sauna and hot tubs are controversial, and fatal outcome is rare, but does happen.

The most intriguing study, considering the risk of death using heat therapy, was a retrospective study which described the epidemiological circumstances and physical findings at autopsy in a total of 268 victims who were found unconscious or dead during hot tubbing in Japan [3]. The results have shown that death was attributed to natural causes in 71% and accidental drowning in 23%, whereas the other 6% died due to unidentified reasons. The reason why acute deaths in a hot bath tub occur with extremely high frequency in Japan remains unknown, but it may be linked to the high temperature of the water (41–42°C) or the advanced age of the patients (between 70 and 90 years). This may explain the majority of the deaths by natural causes. It has been suggested that elderly patients have less ability to control their body temperature [26]. For this reason, the use of lower temperatures for heat therapy in this population may be indicated.

Regarding the miscarriage risk during heat therapy or the risk of structural birth defects, the results suggest that women who use hot tubs more than once during early pregnancy and for long periods have an increased risk of certain birth defect phenotypes [25]. The major conclusion from the studies correlating heat therapy with miscarriage is that pregnant women, during the first 4 weeks from the last menstrual period, should avoid the use of heat therapy [25]. In addition, it is recommended that pregnant women should use heat therapy with temperatures that would maintain their body temperature below 38.9°C [25]. Fertility has also been suggested to be negatively affected by heat therapy; however, studies have shown that sauna bathing does not influence fertility, or if it does, the effect is temporary and reversed immediately after the heat therapy session [27,28].

Allergy, pneumonia, and inflammation have also been reported; however, these are minor reports. For example, the detection of high numbers of *Pseudomonas aeruginosa* in a hot tub indicates massive biofilm formation in the bath circulation [23,24,29]. The increasing popularity of hot tubs demands increased awareness about potential health hazards associated with deficient hygienic maintenance [23,24,29]. For this reason, the use of chemicals to treat the water, such as potassium peroxymonosulfate (PPMS), is normal in pools and hot tubs [30]. Apparently, allergy to PPMS appears to be much more common than previously known [30].

**Table 1.** Provisional guide for the use of heat therapy in obesity and diabetes

| Question | Comments | Final suggestion |
|---|---|---|
| Sauna or hot tub? | Apparently, they are both effective to elevate body temperature and induce beneficial effects. They are also well tolerated. However, considering the risks of allergy and contagious problems reported, sauna may be safer to be used. | Either sauna or hot tub |
| What is the best temperature to use in HT? | The temperature used, well accepted, and considered well tolerated in most studies are, using sauna – 80–100°C (wet sauna-traditional), whereas for hot tub – 40°C, to induce a significant increase in the core temperature. To reach higher core temperatures in humans, the exposure to HT needs to be longer than 50 min. For instance, patients submitted to 50 min bath with increasing water temperature (41°C) can reach a body core temperature of 39°C. However, this temperature may not be well tolerated or comfortable for this population. | 80–100°C (wet sauna); water at 40°C for hot tub; free access to water after the session to avoid dehydration |
| Time of each session? | Most of the trials done in human have found that approximately 15 min is enough to result in cardiovascular and metabolic improvements. | 15 min |
| For how long HT should be used? | The effects of HT have been evaluated in short and long-term therapies, from 2 to 12 weeks. On the basis of the results obtained, we suggest that, for obese and diabetic people, an initial trial of 3 months' therapy, three times per week, should be well tolerated and sufficient to induce benefits in metabolism, cardiovascular function, body composition, and inflammation. | 3 months |

HT, heat therapy.

People with hypertension are commonly warned to check with a physician before using a hot tub, but there is little literature on which to base this advice. However, there are some cardiovascular contraindications for the use of heat therapy, such as severe aortic stenosis, unstable angina pectoris, recent myocardial infarction, decompensated heart failure, and cardiac arrhythmia [1]. Finally, in people with diabetes and using insulin administration, heat therapy may induce the risk of ketoacidosis [1] because plasma concentrations of several counter-regulatory hormones, including growth hormone and glucagon, are increased by exposure to hyperthermia [1] and the risk of hypoglycemia due to enhanced insulin absorption [1].

## A PROVISIONAL GUIDELINE FOR THE USE OF HEAT THERAPY IN DIABETES

If heat therapy is capable of inducing positive modifications on insulin sensitivity, inflammation, reduction of body weight, and fat mass in humans, what is the ideal method? On the basis of the small number of human studies, this question is difficult to answer; however, we are suggesting a provisional method for the use of heat therapy in obesity and

**Table 2.** Contraindications for the use of heat therapy

| Contraindication | Comments |
|---|---|
| Pregnancy | Relative low risk. However, pregnant women, during the first 4 weeks of the last menstrual period, should avoid the use of HT. After this period, pregnant women should use HT with temperatures that would maintain her body temperature below 38.9°C. In case of high-risk pregnancy, HT is not indicated. |
| Anhidrosis or any condition that reduce sweat production | Since anhidrosis creates a dangerous inability to tolerate heat, HT is not indicated. |
| Path delivery system medications | These should be avoid or controlled during HT since increments on skin temperature/blood flow may increase the delivery rate. |
| Unstable cardiovascular diseases | These include: severe aortic stenosis, unstable angina pectoris, recent myocardial infarction, decompensated heart failure, and cardiac arrhythmia. |
| Allergy to potassium peroxymonosulfate (PPMS): for hot tub only | Patients with the highest risk are men between the ages of 45 and 80. This is a relatively easily identifiable cause of widespread, recalcitrant, severe dermatitis, and all patients presenting with this picture should be questioned about hot tub use. |

HT, heat therapy.

diabetes (Table 1). However, prior to the initiation of heat therapy, it is important to make sure that the patient is not within the list of contraindications (Table 2).

## CONCLUSION

Heat therapy is a promising and inexpensive tool to be included in prevention and treatment of sedentary (or unable to perform exercise) obese and diabetic people. We proposed that, the transient increments in the nitric oxide and HSP70 levels may explain the benefits of heat therapy. The limited data in humans suggest that heat therapy may improve patient health, but additional trials are needed to confirm this outcome. Finally, on the basis of the available data, we suggest that heat therapy (traditional sauna: 80–100°C; hot tub: at 40°C) for 15 min, three times per week, for 3 months, is a well tolerated method to test the efficiency of this therapy in this population.

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### Conflicts of interest

*There are no conflicts of interest.*

## REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

1. Crinnion WJ. Sauna as a valuable clinical tool for cardiovascular, autoimmune, toxicant- induced and other chronic health problems. Altern Med Rev 2011; 16:215–225.
2. Hooper PL. Hot-tub therapy for type 2 diabetes mellitus. N Engl J Med 1999; 341:924–925.
3. Satoh F, Osawa M, Hasegawa I, *et al.* Dead in hot bathtub' phenomenon: accidental drowning or natural disease? Am J Forensic Med Pathol 2013; 34:164–168.
4. Beever R. The effects of repeated thermal therapy on quality of life in patients with type II diabetes mellitus. J Altern Complement Med 2010; 16:677–681.
5. Biro S, Masuda A, Kihara T, Tei C. Clinical implications of thermal therapy in lifestyle-related diseases. Exp Biol Med (Maywood) 2003; 228:1245–1249.
6. ■■ Henstridge DC, Whitham M, Febbraio MA. Chaperoning to the metabolic party: The emerging therapeutic role of heat-shock proteins in obesity and type 2 diabetes. Mol Metab 2014; 3:781–793.

In this review, they summarized all data related to HSPs, heat therapy, and diabetes, along with the use of HSP70 inductors.

7. ■■ Hooper PL, Balogh G, Rivas E, *et al.* The importance of the cellular stress response in the pathogenesis and treatment of type 2 diabetes. Cell Stress Chaperones 2014; 19:447–464.

In this review, the importance of the heat shock response in the context of type 2 diabetes was discussed.

8. ■ Krause M, Heck TG, Bittencourt A, *et al.* The Chaperone Balance Hypothesis: the importance of the extracellular to intracellular HSP70 ratio to inflammation-driven type 2 diabetes, the effect of exercise, and the implications for clinical management. Mediators Inflamm 2015. [Epub ahead of print]

In this review, the importance of the eHSP70/iHSP70 ratio in the context of type 2 diabetes was discussed.

9. Rodrigues-Krause J, Krause M, O'Hagan C, *et al.* Divergence of intracellular and extracellular HSP72 in type 2 diabetes: does fat matter? Cell Stress Chaperones 2012; 17:293–302.
10. ■■ Krause M, Keane K, Rodrigues-Krause J, *et al.* Elevated levels of extracellular heat-shock protein 72 (eHSP72) are positively correlated with insulin resistance in vivo and cause pancreatic beta-cell dysfunction and death in vitro. Clin Sci (Lond) 2014; 126:739–752.

In this study, it was demonstrated that extracellular HSP72 is correlated with inflammation and insulin resistance in the elderly, and that chronic exposure of pancreatic beta cells to eHSP70 induces cell dysfunction and death.

11. Newsholme P, Krause M. Diet, obesity, and reactive oxygen species: implications for diabetes and aging. Syst Biol Free Radic Antioxidants 2014; 01:3361–3374.
12. Newsholme P, Rebelato E, Abdulkader F, *et al.* Reactive oxygen and nitrogen species generation, antioxidant defenses, and beta-cell function: a critical role for amino acids. J Endocrinol 2012; 214:11–20.
13. Newsholme P, de Bittencourt PI Jr. The fat cell senescence hypothesis: a mechanism responsible for abrogating the resolution of inflammation in chronic disease. Curr Opin Clin Nutr Metab Care 2014; 17:295–305.
14. Ohno Y, Yamada S, Sugiura T, *et al.* A possible role of NF-kappaB and HSP72 in skeletal muscle hypertrophy induced by heat stress in rats. Gen Physiol Biophys 2010; 29:234–242.
15. Karpe PA, Tikoo K. Heat shock prevents insulin resistance-induced vascular complications by augmenting angiotensin-(1-7) signaling. Diabetes 2014; 63:1124–1139.
16. Johnson JM, Kellogg DL Jr. Thermoregulatory and thermal control in the human cutaneous circulation. Front Biosci (Schol Ed) 2010; 2:825–853.
17. Caro AC, Hankenson FC, Marx JO. Comparison of thermoregulatory devices used during anesthesia of C57BL/6 mice and correlations between body temperature and physiologic parameters. J Am Assoc Lab Anim Sci 2013; 52:577–583.
18. Low DA, Keller DM, Wingo JE, *et al.* Sympathetic nerve activity and whole body heat stress in humans. J Appl Physiol 2011; 111:1329–1334.
19. Pilch W, Szygula Z, Palka T, *et al.* Comparison of physiological reactions and physiological strain in healthy men under heat stress in dry and steam heat saunas. Biol Sport 2014; 31:145–149.
20. Malyshev I, Bayda LA, Trifonov AI, *et al.* Cross-talk between nitric oxide and HSP70 in the antihypotensive effect of adaptation to heat. Physiol Res 2000; 49:99–105.
21. Krause M, Rodrigues-Krause J, O'Hagan C, *et al.* Differential nitric oxide levels in the blood and skeletal muscle of type 2 diabetic subjects may be consequence of adiposity: a preliminary study. Metabolism 2012; 61:1528–1537.
22. ■■ Krause M, Bock PM, Takahashi HK, *et al.* The regulatory roles of NADPH oxidase, intra and extracellular HSP70 in pancreatic islet function, dysfunction and diabetes. Clin Sci [Review] 2015; 128:789–803.

In this review, the role of HSP70 in the pancreatic α and β cells is discussed.

23. Fjallbrant H, Akerstrom M, Svensson E, Andersson E. Hot tub lung: an occupational hazard. Eur Respir Rev 2013; 22:88–90.
24. Kubin ME, Riekki R. Allergic contact eczema caused by exotic wood material in sauna interior decoration. Contact Dermatitis 2014; 70:255–256.
25. Duong HT, Shahrukh Hashmi S, Ramadhani T, *et al.* Maternal use of hot tub and major structural birth defects. Birth Defects Res A Clin Mol Teratol 2011; 91:836–841.
26. Sawatari H, Chishaki A, Miyazono M, *et al.* Different physiological and subjective responses to the hyperthermia between young and older adults: basic study for thermal therapy in cardiovascular diseases. J Gerontol A Biol Sci Med Sci 2014. [Epub ahead of print]
27. Garolla A, Torino M, Sartini B, *et al.* Seminal and molecular evidence that sauna exposure affects human spermatogenesis. Hum Reprod 2013; 28:877–885.
28. Jurewicz J, Radwan M, Sobala W, *et al.* Lifestyle and semen quality: role of modifiable risk factors. Syst Biol Reprod Med 2014; 60:43–51.
29. Kubin M, Riekki R. Contact allergy to western red cedar in sauna furnishing. Contact Dermatitis 2013; 69:121–122.
30. Gilligan P, Horst AV. Allergy to a hot tub water treatment chemical: an unexpectedly common cause of generalized dermatitis in men. J Clin Aesthet Dermatol 2010; 3:54–56.