

Original Article

# Thermotherapy as an alternative to exercise for metabolic health in obese postmenopausal women: focus on circulating irisin level

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**ABSTRACT** Irisin is a myokine caused by exercise that improves insulin resistance and weight loss. However, under unfavorable conditions such as air pollution, and during the pandemic, outdoor activities are uncomfortable. Therefore, in this study, the effect of heat therapy (half bath  $42 \pm 0.5^\circ\text{C}$  for 30 min) on irisin circulation levels as an exercise alternative for middle-aged obese women after menopause was investigated. Subjects were 33 women aged  $49.54 \pm 6.04$  years, with parameters of height,  $160.12 \pm 4.33$  cm, weight,  $69.71 \pm 7.52$  kg, body surface area  $1.73 \pm 0.13$  m<sup>2</sup>, body mass index,  $27.19 \pm 3.40$  kg/m<sup>2</sup>. The results suggest that circulating irisin levels showed a significant increase after one-time thermotherapy (TH-1). However, the increase in circulating irisin levels after 15 treatments (TH-15, 5 days/week, 3 weeks) was significantly varied. The level of adiponectin, which increases fatty oxidation to reduce fatty deposition, increased significantly at TH-1, but further increased at TH-15, which was significantly different from the level of TH-1. In addition, the basic serum free fatty acid (FFA) level was significantly increased at TH-15 compared to TH-1. Significant differences were also found in the lipid profile (body mass index, waist circumference, and % body fat). Thermotherapy can significantly increase the tympanic temperature and induce changes in circulating irisin and adiponectin levels. Thus, it resulted in positive changes in FFA and lipid profiles. Therefore, repeated thermotherapy is effective in increasing circulating irisin levels in postmenopausal obese women.

## INTRODUCTION

Although the average age at which women undergo menopause in Korea has been reported to be approximately 49 years [1], the median age at menopause throughout the world ranges between 46 and 52 years [2]. Considering that life expectancy is gradually increasing, the postmenopausal period can account for > 40% of the life cycle. It is anticipated that there will be 1.1 billion women aged > 50 years worldwide by 2025 [3]. The health challenges associated with metabolic syndrome after menopause is a global concern that transcends countries, regions, and races.

The high incidence of insulin resistance, metabolic syndrome, and cardiovascular diseases in middle-aged women with menopause is closely related to abdominal obesity [4]. In terms of populations (e.g., Asian vs. non-Asians), Asians with a specified body mass index (BMI) carry higher rates of body fat, abdominal obesity, intramyocellular lipids, and liver fat content than Caucasians, which suggests that Asians have a higher insulin resistance even with low BMI [5]. As the secretion of endogenous estrogen after menopause decreases, the prevalence of metabolic syndrome increases [6]. However, treatment with estrogen preparations is not considered a fundamental strategy [7].



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Researchers have recently started focusing on obesity-related studies because irisin is an exercise-induced myokine that reduces fat and improves glucose metabolism [8]. Irisin is a proteolytic cleavage product of fibronectin type III domain-containing protein 5 (FNDC5) protein in skeletal muscles [8]. It promotes energy consumption by causing browning of white adipose tissue [9]. Aerobic exercise is effective in increasing the level of circulating irisin in middle-aged and older groups and reducing the amount of systemic fat and abdominal visceral adipose tissue [10]. Therefore, aerobic exercise may be an important strategy to increase FNDC5 gene expression, even in postmenopausal women. Previous study has shown that thermotherapy induces oxidative stress and increases circulating irisin levels [11]. It is known that completely evaporated sweat is equivalent to 580 kcal of heat energy being removed from the body [12-14]. This suggests that thermotherapy has effects similar to exercising.

Exercise environment is important. Although exercise is a strategy to prevent obesity and significantly improve quality of life by enhancing immune system in women after menopause [15,16], aerobic exercise may be limited by the environmental variables and the effects of infectious diseases.

Yale University presented the findings of the Environmental Performance Index in 2018 by setting nine criteria, such as air quality and health consequences, based on 19 indices for 180 countries. Among the three countries in the Far East Asia, Japan ranks relatively higher in at 20th in terms of environmental performance, whereas Korea ranked 60th and China 120th [17]. In a study of 71,431 men in 25 major cities in China, it was found that mortality related to cardio-respiratory diseases increased with exposure to particulate air pollution [18]. According to the levels of national air pollution provided by the Korea Environment Corporation (Air Korea) in real time [19], the number of domestic fine dust (mixture of particles < 10  $\mu\text{m}$  [0.01 mm] from various sources) [20] advisories issued in 17 major cities and provinces, including Seoul, the capital of Korea, is gradually increasing (Supplementary Fig. 1A). Moreover, as the number of hot days increases, the number of people with heat-related illnesses also increases (Supplementary Fig. 1B). There is no universal definition of a heat wave; however, such extreme events associated with hot temperature in summer have been known to impact human mortality [21,22].

In addition, a new coronavirus (COVID-19), which was recently been reported to cause symptoms similar to pneumonia in Wuhan, China, has begun to spread worldwide. The World Health Organization has declared it a pandemic. COVID-19 belongs to a large family of viruses that are known to be transmitted from animals to humans, causing diseases similar to Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS). Outdoor workout is limited by because the highly contagious COVID-19, which has spread more rapidly across the world than the combination of SARS and MERS. Thus, recent suggestions have focused on strategies to maintain

a healthy lifestyle and to protect public health while minimizing the negative effects of environmental variables [23].

The above environmental health and outdoor environment problems raise the need for research on the effects of thermotherapy. Therefore, this study examined the benefits of repeated thermotherapy (15 times) for circulatory levels of irisin, adiponectin and lipids (BMI, waist circumference and body fat ratio), biomarkers that affect body temperature control in postmenopausal obese women among residents of increasing environmental restrictions.

## METHODS

### Subjects

The subjects were 33 postmenopausal obese women (age,  $49.54 \pm 6.04$  years; height,  $160.12 \pm 4.33$  cm; weight,  $69.70 \pm 7.52$  kg; body surface area,  $1.73 \pm 0.13$  m<sup>2</sup>; (%) body fat,  $32.75 \pm 4.06$ ; body mass index,  $27.19 \pm 3.40$  kg/m<sup>2</sup>; waist size,  $85.92 \pm 8.10$  cm, and tympanic temperature,  $36.61 \pm 0.31^\circ\text{C}$ ) who volunteered to participate in the experiment at the College of Medicine of Soonchunhyang University in Cheonan, Republic of Korea. All participants resided in Chenoan (Republic of Korea), and were nonsmokers, sedentary, and not exposed to estrogen replacement therapy. Subjects were asked to sign the informed consent regarding the study purpose and procedures. All procedures complied with the 2013 Helsinki Declaration of the World Medical Association and approved by the Institutional Review Board on Human Subjects Research and Ethics Committees, Soonchunhyang University (No. 1040875-201611-BR-042), Cheonan, Republic of Korea.

### Measurement and experimental procedure

Subjects completed their lunch as usual and were instructed to arrive in the waiting room by 2 pm for the experiment. The core temperature was checked by using a TSK7+1 thermistor probe (Songkitopia, Incheon, Korea) and a K923 small spring (Takara, Yokohama, Japan) before the thermotherapy for 1–15 sessions. The probe was connected to a CF-T1 personal computer (Panasonic, Tokyo, Japan) and a K-720 data logger (Technol Seven, Yokohama, Japan). When the body temperature was  $36^\circ\text{C}$ – $37^\circ\text{C}$ , subjects were asked to consume 5–7 ml/kg of water.

After resting in a sitting position for 60 min in the laboratory, physical parameters including height, weight, BMI, whole body sweat loss volume and percentage of body fat were automatically measured using Inbody equipment (InBody 770; InBody Co., Seoul, Korea). The waist circumference was directly measured by a researcher.

Next, blood was collected, and thermotherapy was applied for 60 min. The subjects who completed thermal treatment were immediately subjected to tympanic temperature ( $T_{\text{ty}}$ ) and blood col-

lection again. Although heat treatment was similarly repeated 15 times, body measurements and blood collection were performed only before (pre) and after (post the first [TH-1] and 15th [TH-15] thermotherapy. Five-minute breaks in the chamber air temperature were provided every after 5 min of heat loading (Fig. 1) [11]. Intake of alcoholic or caffeine-containing beverages or food and strenuous physical activity was avoided 24 h before the experiment and subjects were asked to sleep for at least 8 h a day during the experiment.

### Tympanic temperature ( $T_{ty}$ ) and mean body temperature ( $mT_b$ ) measurements

$T_{ty}$  was assessed continuously at 10-sec intervals for 60 min in the left ear by inserting a thermistor probe (TSK7+1; Songkitopia) with a small spring (K923; Takara) connected to a personal computer (CF-T1; Panasonic) and a data logger (K-720; Technol Seven) [24-27]. When the thermistor probe contacted the tympanic membrane, the subject felt slight discomfort and could hear a scratching noise. The inner pinna was filled with small cotton balls to fix the probe in the ear [11,24-27].

Skin temperatures of the chest ( $T_{s_{chest}}$ ), upper arm ( $T_{s_{arm}}$ ), thigh ( $T_{s_{thigh}}$ ), and leg ( $T_{s_{leg}}$ ) were measured (continuous assessment, Fig. 1) with a TSK7+1 thermistor probe (Songkitopia) and a K923 small spring (Takara) [24-27]. The probe was connected to a CF-T1 personal computer (Panasonic) and a K-720 data logger (Technol Seven). Mean skin temperature ( $mTs$ ) was calculated using the Ramanathan equation [28]. The parameter  $mT_b$  was calculated using the formula of Sugeno and Ogawa [29]:  $mT_b = (0.9 \cdot T_{ty} + 0.1 \cdot mTs)$ .

### Thermotherapy

Thermotherapy was conducted in the city of Cheonan (Chungnam), Republic of Korea. Cheonan is located in the southwest part of Korea (126°52'N, 33.38'E) and extends to the northeast (130°4'N, 43.0'E). The test conditions were maintained at  $26.5 \pm 0.3^\circ\text{C}$  and relative humidity of  $60 \pm 0.3\%$  with an air velocity of 1 m/s. Thermotherapy involved immersing half the body

(up to the belly button) into a hot water bath at a temperature of  $42 \pm 0.5^\circ\text{C}$  for 60 min similar to conditions reported in previous studies [26,30,31]. However, considering that the subjects were middle-aged, continuous thermotherapy for 30 min was avoided. Although the thermotherapy was conducted for 60 min, the treatment was stopped every 5 min, and the subjects were instructed to emerge out of the hot water bath and rest for 5 min. A 5-min break was provided after 5, 10, 15, 20, 25, and 30 min of heat loading to minimize possible discomfort during physical immersion. Additionally, a drinkable 500 ml of tepid ( $25.0 \pm 0.5^\circ\text{C}$ ) water bottle was provided for each subjects to prevent dehydration (Fig. 1) [11]. Thus, the actual heat loading was applied for 30 min, and all subjects were exposed to 15 rounds of treatment (5 day/week, for 3 weeks) (conducted once a day and every other day). The experimental period ranged from January 3, 2018 to February 2, 2018 (Supplementary Fig. 2). All subjects wore shorts and short-sleeved shirts provided by the researchers.

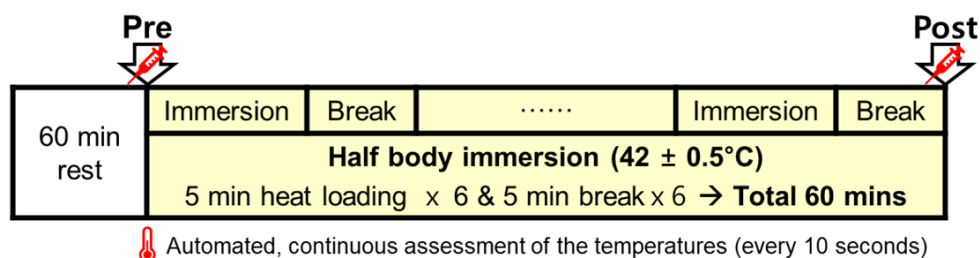
### Waist circumference (WC)

Before measuring WC, subjects were made to stand upright while breathing lightly. In this posture, the waist size was measured with a tapeline held horizontally at the mid-portion between lowermost part of rib and uppermost part of iliac crest. Care was taken not to press the skin. WC was measured to the nearest 0.1 cm by a single experienced researcher [32].

### Basal metabolic rate (BMR)

Subjects were asked to fast for 12 h and sleep for at least 8 h the night before testing.

The protocol consisted of 10 min of bed rest in the supine position followed by analysis of expired gas samples for 30 min. A computerized gas analyzer (Quark PFT; Cosmed, Rome, Italy) was used to determine oxygen uptake ( $\text{VO}_2$ ) and carbon dioxide output ( $\text{VCO}_2$ ). BMR was calculated by following formula;  $[(3.9 \times \text{VO}_2) + (1.1 \times \text{VCO}_2)] \times 1,440$  [33].



**Fig. 1. Schematic representation of the experimental protocol condition in air temperature  $25.0 \pm 0.5^\circ\text{C}$  and relative humidity  $60.0 \pm 3.0\%$ .** Heat stimulation entailed immersing half of the body into a hot water bath ( $42 \pm 0.5^\circ\text{C}$ ) for total 30 min and break for total 30 min. Blood sampling was done before immersion (Pre) and immediately after the last break (Post). Tympanic and local skin temperature measurements were conducted continuously at 10-sec intervals for 60 min.

## Whole-body sweat loss volume

Body weight loss after half-body immersion can be caused by sweating. Body weight was therefore measured before and after immersion with a precision instrument (IW2, Sartorius, Germany) to determine the whole-body sweat loss volume [31].

## Blood analysis

Blood samples were collected at before and after experiment in TH-1 and TH-15. Blood samples were collected in a serum separator tube from the antecubital vein and left at room temperature for 15–30 min to enable clotting, after which the samples were centrifuged at 3,000 rpm (2,000 ×g) and 4°C for 10 min. Serum was then harvested and stored at –80°C until analysis. Irisin was determined using a commercial ELISA kit (Irisin EIA kit EK-067–16; Phoenix Pharmaceuticals, Burlingame, CA, USA) with a spectrophotometric reader. Adiponectin was measured using a commercial Microplate Reader (USA) ELISA with a spectrophotometric reader. Serum free fatty acids (FFA) were analyzed using a model 7180 automated analyzer (Hitachi, Tokyo, Japan).

## Statistical analysis

Descriptive statistics are expressed as mean ± standard deviation (SD) using the commercially-available computer software SPSS for Windows, version 21.0 (IBM Co., Armonk, NY, USA). Normality of the data were verified via Shapiro–Wilk normality test followed by calculating skewness and kurtosis of the statistics. Statistical significance was determined using student t-test and paired t-test to conduct a comparison between TH-1 (Pre vs. Post) and TH-15 (Pre vs. Post) heat stimulation. Linear regression analysis and Pearson correlation coefficient were used to assess the correlations between variables. Significant differences were considered at  $p < 0.05$ .

## RESULTS

### Tympanic temperature ( $T_{ty}$ )

$T_{ty}$  increased significantly in TH-1 (Pre,  $36.61 \pm 0.31^\circ\text{C}$  vs. Post,  $38.48 \pm 0.33^\circ\text{C}$ ) and TH-15 (Pre,  $36.79 \pm 0.33$  vs. Post,  $38.75 \pm 0.34^\circ\text{C}$ ) ( $***p < 0.001$ ). Particularly,  $T_{ty}$  after TH-15 was significantly higher than TH-1 (Pre,  $\Delta T_R = 0.18^\circ\text{C}$ ,  $^{\#}p < 0.05$ ; Post,  $\Delta T_P \text{ post} = 0.27^\circ\text{C}$ ,  $^{\#}p < 0.05$ ) (Fig. 2A).

### BMR

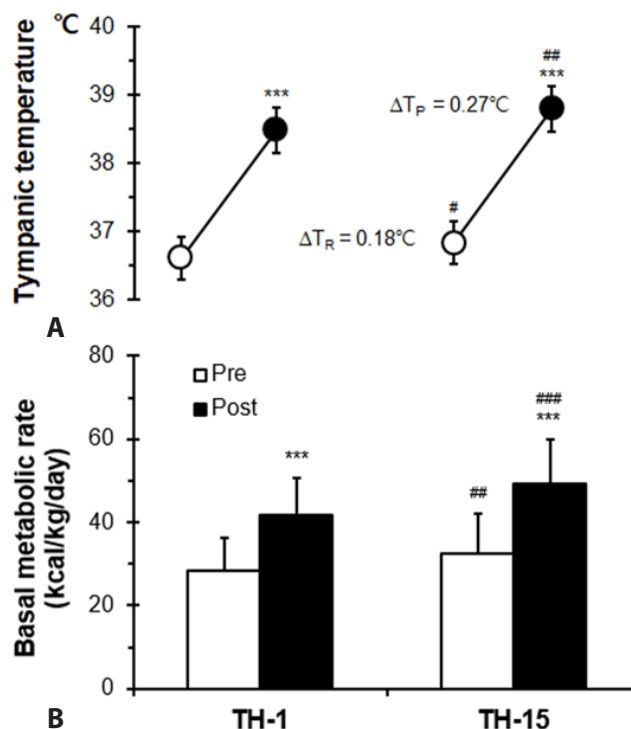
As shown in Fig. 2B, BMRs were higher in TH-15 than in TH-1 before ( $^{\#}p < 0.01$ ) and after ( $^{\#}p < 0.001$ ) the heat load test, respectively. After heat load, BMRs were increased by 13.35 kcal/kg/day

( $***p < 0.001$ ) in TH-1 and 16.91 kcal/kg/day ( $***p < 0.001$ ) in TH-15.

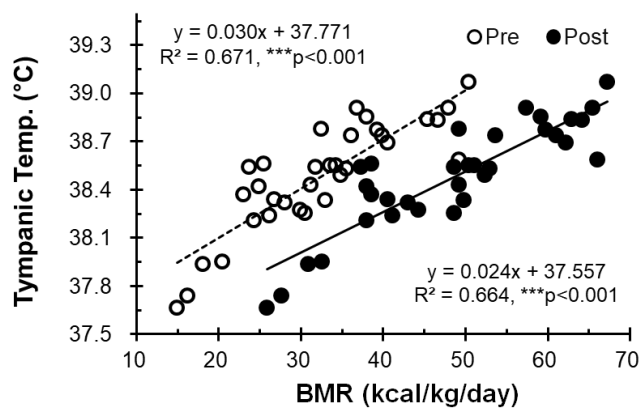
Correlation between  $T_{ty}$  and BMR before and after half-body immersion protocol is shown in Fig. 3. A positive relationship between  $T_{ty}$  and BMR was observed before ( $R^2 = 0.671$ ,  $***p < 0.001$ ) and after ( $R^2 = 0.664$ ,  $***p < 0.001$ ) hot water treatment was also observed.

### Irisin

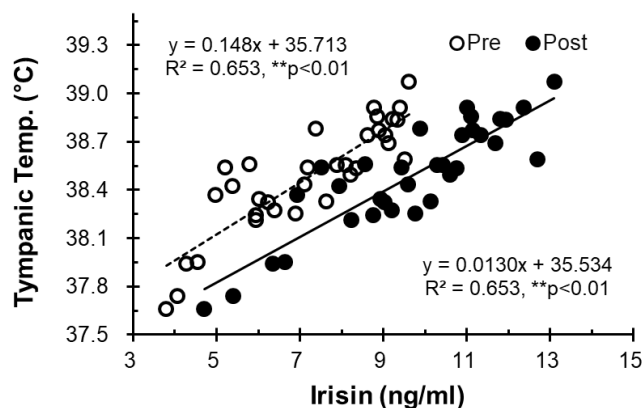
The levels of circulating irisin increased significantly after thermotherapy (TH-1, Pre,  $6.05 \pm 1.59$  ng/ml vs. Post,  $7.92 \pm 1.82$  ng/ml,  $***p < 0.001$ ; TH-15, Pre,  $7.24 \pm 1.44$  ng/ml vs. Post,  $9.65 \pm 2.01$  ng/ml,  $***p < 0.001$ ). The circulating irisin levels before and after TH-15 showed significant difference compared with that of TH-1, respectively (Pre,  $^{\#}p < 0.01$ ; Post,  $^{\#}p < 0.01$ ) (Fig. 4).



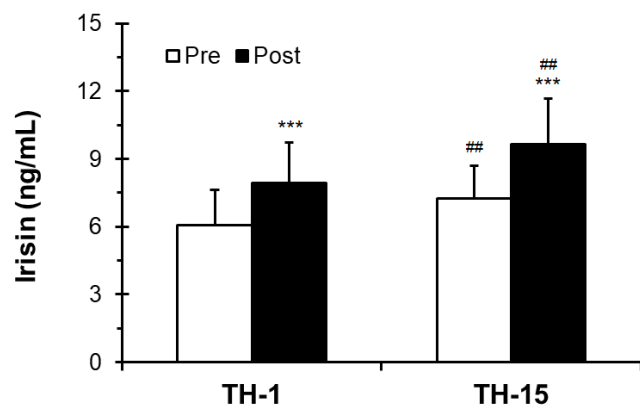
**Fig. 2. Tympanic temperature and basal metabolic rate.** (A) Tympanic temperature, Pre (white circle) and Post (black circle), (B) basal metabolic rate (BMR), Pre (white bar) and Post (black bar) on thermotherapy. TH-1 (pre □:  $28.27 \pm 8.06$  kcal/kg/day vs. post ■:  $41.62 \pm 9.13$  kcal/kg/day,  $***p < 0.001$ ) and TH-15 (pre □:  $32.41 \pm 9.52$  kcal/kg/day vs. post ■:  $49.32 \pm 10.64$  kcal/kg/day,  $***p < 0.001$ ) for differences between Pre vs. Post.  $^{\#}p < 0.01$ ,  $^{\#}p < 0.01$ , and  $^{\#}p < 0.001$  for difference between TH-1 and TH-15. Values ( $n = 33$ ) are mean ± SD. Resting BMR of TH-15 was significantly higher than in TH-1 (before thermotherapy,  $28.27 \pm 8.06$  kcal/kg/day vs.  $41.62 \pm 9.13$  kcal/kg/day,  $^{\#}p < 0.01$ ). BMR was increased by 13.35 kcal/kg/day ( $***p < 0.001$ ) in TH-1 and by 16.91 kcal/kg/day ( $***p < 0.001$ ) in TH-15. TH, thermotherapy, immersing half-bath,  $42 \pm 0.5^\circ\text{C}$  for 60 min (5-min break at 5-min intervals); TH-1, application of thermotherapy once; TH-15, application of thermotherapy repeated 15 times.



**Fig. 3.** Correlation between the tympanic temperature and basal metabolic rate (BMR) before (Pre; ○) and after (Post; ●) hot water bath ( $42 \pm 0.5^\circ\text{C}$ ) immersion at TH-15. TH, thermotherapy. \*\*\* $p < 0.001$ , statistically significant difference (Pre;  $R^2 = 0.671$ , Post;  $R^2 = 0.664$ ).



**Fig. 5.** Correlation between the tympanic temperature and irisin concentration before (Pre; ○) and after (Post; ●) hot water bath ( $42 \pm 0.5^\circ\text{C}$ ) immersion at TH-15. TH, thermotherapy. \*\* $p < 0.01$ , statistically significant difference (Pre;  $R^2 = 0.653$ , Post;  $R^2 = 0.653$ ).

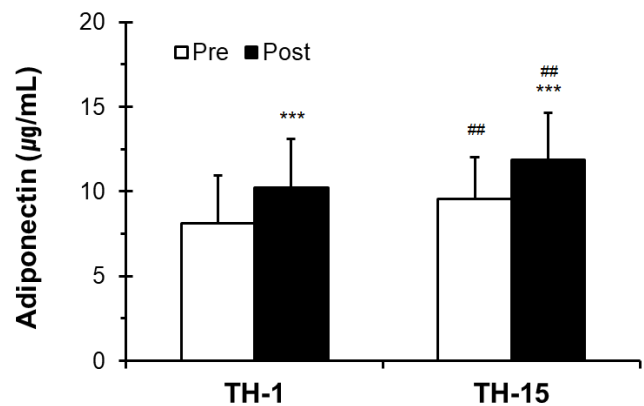


**Fig. 4.** Changes in the levels of irisin following thermotherapy. Values ( $n = 33$ ) are mean  $\pm$  SD. Changes in the levels of circulating irisin. Statistically significant differences were found between Pre and Post, \*\*\* $p < 0.001$ , and significant differences between TH-1 and TH-15, ## $p < 0.01$ . TH, thermotherapy, immersing half-bath,  $42 \pm 0.5^\circ\text{C}$  for 60 min (5-min break at 5-min intervals); TH-1, application of thermotherapy once; TH-15, application of thermotherapy repeated 15 times.

Correlation between  $T_{ty}$  and irisin levels before and after half-body immersion protocol is shown in Fig. 5. A positive relationship between  $T_{ty}$  and irisin levels was observed before ( $R^2 = 0.653$ , \*\* $p < 0.01$ ) and after ( $R^2 = 0.653$ , \*\* $p < 0.01$ ) hot water treatment was also observed.

### Adiponectin

The levels of circulating adiponectin increased significantly after thermotherapy (TH-1; Pre,  $8.13 \pm 2.80 \mu\text{g/ml}$  vs. Post,  $10.24 \pm 2.85 \mu\text{g/ml}$ , \*\*\* $p < 0.001$ ; TH-15; Pre,  $9.57 \pm 2.47 \mu\text{g/ml}$  vs. Post,  $11.86 \pm 2.76 \mu\text{g/ml}$ , \*\*\* $p < 0.001$ ), and the levels of circulating adiponectin after TH-15 showed a significant difference compared with those after TH-1 (Pre, ## $p < 0.01$ ; Post, ## $p < 0.01$ ) (Fig. 6).



**Fig. 6.** Changes in adiponectin levels based on thermotherapy. Values ( $n = 33$ ) are mean  $\pm$  SD. Statistically significant differences were found between Pre and Post, \*\*\* $p < 0.001$ , and significant differences between TH-1 and TH-15, ## $p < 0.01$ . TH, thermotherapy, immersing half-bath,  $42 \pm 0.5^\circ\text{C}$  for 60 min (5-min break at 5-min intervals); TH-1, application of thermotherapy once; TH-15, application of thermotherapy repeated 15 times.

### FFA

The levels of circulating FFA increased significantly after thermotherapy (TH-1; Pre,  $467.15 \pm 148.96 \mu\text{Eq/L}$  vs. Post,  $551.64 \pm 164.53 \mu\text{Eq/L}$ , \*\*\* $p < 0.001$ ; TH-15; Pre,  $532.38 \pm 124.37 \mu\text{Eq/L}$  vs. Post,  $627.25 \pm 149.28 \mu\text{Eq/L}$ , \*\*\* $p < 0.001$ ), and the levels of circulating FFA after TH-15 showed a significant difference compared with those after TH-1 (Pre, ## $p < 0.01$ ; Post, ## $p < 0.01$ ) (Fig. 7).

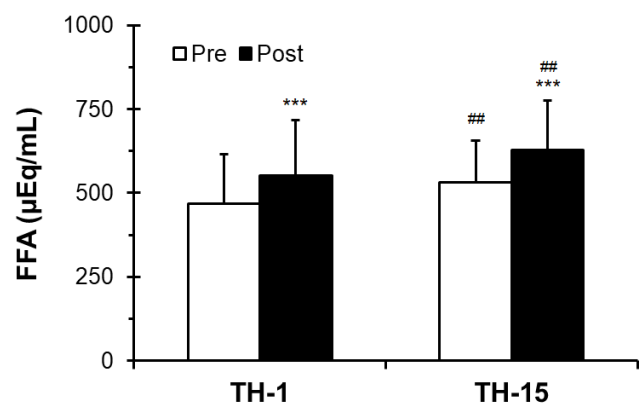
### Whole body sweat loss volume

As shown in Fig. 8, subjects in TH-1 lost a total sweat output of  $564 \pm 208 \text{ ml}$ , whereas those after TH-15 lost a total sweat output

of  $712 \pm 225$  ml. The difference in whole body sweat loss volume between the TH-1 and TH-15 (increase rate of 26.24%) was statistically significant ( $^{***}p < 0.001$ ).

### BMI, WC, % body fat (TH-1, Pre vs. TH-15, Post)

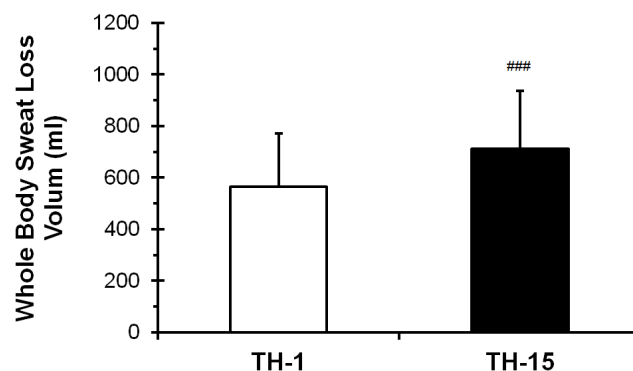
The levels of BMI decreased significantly after thermotherapy (TH-1, Pre vs. Post,  $^*p < 0.05$ ; TH-15, Pre vs. Post,  $^{**}p < 0.01$ ), and there was a significant difference between TH-15 and TH-1 (Pre,  $^{\#}p < 0.05$ ; Post,  $^{###}p < 0.001$ ). WC significantly decreased after thermotherapy (TH-1, Pre vs. Post,  $^{**}p < 0.01$ ; TH-15, Pre vs. Post,  $^{***}p < 0.001$ ), and showed a significant difference between the two treatments (Pre,  $^{\#}p < 0.05$ ; Post,  $^{###}p < 0.001$ ). The percentage of body fat also decreased significantly after thermotherapy (TH-1, Pre vs. Post,  $^*p < 0.05$ ; TH-15, Pre vs. Post,  $^{***}p < 0.001$ ), with a significant difference between the two treatments (Pre,  $^{\#}p < 0.01$ ; Post,  $^{###}p < 0.001$ ) (Table 1). Thus, single exposure to TH-1 resulted in significantly reduced obesity indices.



**Fig. 7. Changes in the levels of free fatty acids (FFA) based on thermotherapy.** Values ( $n = 33$ ) are mean  $\pm$  SD. Statistically significant differences were found between Pre and Post,  $^{***}p < 0.001$ , and significant differences were found between TH-1 and TH-15,  $^{\#}p < 0.01$ . TH, thermotherapy, immersing half-bath,  $42 \pm 0.5^{\circ}\text{C}$  for 60 min (5-min break at 5-min intervals); TH-1, application of thermotherapy once; TH-15, application of thermotherapy repeated 15 times.

## DISCUSSION

Irisin is a substance released from muscle tissue in response to exercise and low-temperature environments [34]. It improves insulin resistance and reduces weight [8]. However, considering the recent environmental factors in Korea, outdoor exercises are restricted to obese women after menopause. Half bath is a type of bath culture popular among Koreans, and its application is simple. Hence, this study used thermotherapy via repeated half-bath using hot water as a strategy to replace exercise and minimize fat accumulation in obese women after menopause. Furthermore, it has been already known that high temperatures lead to oxidative stress [35]. Recently, study with women subjects has shown that thermotherapy can upregulate circulating irisin level by inducing oxidative stress [11]. In our study, it can be seen that the circulating irisin level rose before and after treatment during the first thermotherapy (TH-1, Pre,  $6.05 \pm 1.59$  ng/ml vs. Post,  $7.92 \pm 1.82$  ng/ml,  $^{***}p < 0.001$ ), and the base line increased during the last thermotherapy (TH-15, Pre,  $7.24 \pm 1.44$  ng/ml vs. Post,  $9.65 \pm 2.01$  ng/ml,  $^{***}p < 0.001$ , Fig. 4). Increment of oxidative stress markers that elevated after thermotherapy were positively related with the increase in circulating irisin concentration. This is consistent with findings of Samy *et al.* [36] that muscle damage and oxidative



**Fig. 8. Changes in the levels of whole body sweat loss volume based on thermotherapy.** Values ( $n = 33$ ) are mean  $\pm$  SD. Statistically significant differences between TH-1 and TH-15 ( $^{###}p < 0.001$ ). TH, thermotherapy, immersing half-bath,  $42 \pm 0.5^{\circ}\text{C}$  for 60 min (5-min break at 5-min intervals); TH-1, application of thermotherapy once; TH-15, application of thermotherapy repeated 15 times.

**Table 1. Changes in obesity indices after thermotherapy**

Variable	TH-1		TH-15	
	Pre	Post	Pre	Post
BMI ( $\text{kg}/\text{m}^2$ )	$27.19 \pm 3.40$	$26.81 \pm 3.05^*$	$25.84 \pm 3.12^{\#}$	$25.31 \pm 3.17^{**\#\#}$
WC (cm)	$85.43 \pm 8.12$	$84.27 \pm 8.30^{**}$	$83.49 \pm 7.25^{\#}$	$82.14 \pm 7.30^{***\#\#}$
% Body fat	$32.75 \pm 4.06$	$32.29 \pm 4.12^*$	$31.35 \pm 3.51^{\#\#}$	$30.67 \pm 3.61^{***\#\#}$

Values ( $n = 33$ ) are means  $\pm$  SD. TH, thermotherapy, half-bath,  $42 \pm 0.5^{\circ}\text{C}$  for 60 min (5-min break at 5-min intervals); TH-1, application of thermotherapy once; TH-15, application of thermotherapy 15 times; BMI, body mass index (calculated from height and weight,  $\text{BMI} = \text{weight (kg)} / [\text{height (m)} \times \text{height (m)}]$ ); WC, waist circumference. Statistically significant differences were found between Pre and Post,  $^*p < 0.05$ ,  $^{**}p < 0.01$ ,  $^{***}p < 0.001$ , and significant differences between TH-1 and TH-15,  $^{\#}p < 0.05$ ,  $^{\#\#}p < 0.01$ ,  $^{\#\#\#}p < 0.001$ .

stress were related to irisin concentration. The result of this study showed that the positive relationships between the concentration of irisin and  $T_{ty}$  [11] (\*\* $p < 0.01$ , Fig. 5). Therefore, this study suggests that thermotherapy induces oxidative stress in middle-aged women after menopause, resulting in increased levels of circulating irisin. This study found that the levels of circulating irisin, adiponectin, and FFA increased significantly after repeated thermotherapy (15 sessions) for 3 weeks. In addition, the significant increase in sweat volume loss of 26.24% in TH-15 ( $712 \pm 225$  ml) compared to TH-1 ( $564 \pm 208$  ml) explains that thermotherapy resulted in increased basal metabolism and similar energy consumption to exercise [14]. Therefore, in this study, BMI, WC and percentage of body fat significantly decreases similar to exercise during thermal therapy. Despite the several differences depending on the type of exercise, exercise in general induces the expression of irisin/FNDC5 [8,37], which is strongly related to modulate the physiological or pathophysiological response to environmental, metabolic, emotional, and psychological stimuli [38]. From this point of view, thermotherapy also increased circulating irisin levels to respond to oxidative stress, similar to exercise [11]. Thermotherapy is valuable as an alternative treatment for menopause women due to a decrease in the amount of exercise due to restrictions on outdoor activities. The major factors contributing to excessive fat accumulation in middle-aged women are aging, decreased physical activity, and reduced muscle mass (sarcopenia), which decrease the metabolic rate [39-41]. Adipose tissue not only stores lipids but also functions as a paracrine and endocrine organ. It also secretes adiponectin to promote fat oxidation in skeletal muscles and inhibits hepatic glucose production to improve systemic energy homeostasis [42]. Furthermore, it reduces inflammation in various cells, such as those in the vasculature, heart, lung, and colon, via AdipoR1 and R2 receptor signaling, anti-inflammatory and anti-apoptotic mechanisms [43]. Because adiponectin enhances lipid profile [44], it is also used as an objective index to explain the correlation between central obesity and insulin resistance [45]. Our study also confirmed an increase in adiponectin during thermotherapy, which can be seen that thermotherapy leads to metabolic improvement (TH-1; Pre,  $8.13 \pm 2.80$   $\mu\text{g/ml}$  vs. Post,  $10.24 \pm 2.85$   $\mu\text{g/ml}$ , \*\*\* $p < 0.001$ ; TH-15; Pre,  $9.57 \pm 2.47$   $\mu\text{g/ml}$  vs. Post,  $11.86 \pm 2.76$   $\mu\text{g/ml}$ , \*\*\* $p < 0.001$ , Fig. 6). A significant increase in adiponectin depending on environmental conditions may be a predictor of increased activity of brown adipose tissue [46]. In addition, the levels of plasma adiponectin decrease in obesity and diabetes [47].

Therefore, repeated thermotherapy in postmenopausal middle-aged women was effective in increasing the levels of circulating irisin and adiponectin and in improving lipid profile. Studies investigated the preventive effects of bathing against hypertension, hyperlipidemia, and depression [48-50]. However, this study is the first of its kind to measure the levels of circulating irisin and to show that thermotherapy can be an alternative to exercise in increasing the levels of circulating irisin.

Thermotherapy is economical, and unlike medical treatment, it is a preventive concept and is meaningful in that it is highly accessible and convenient. Based on the individual physical characteristics, lifestyle, and presence of disease, thermotherapy can be implemented under various conditions. Repeated thermotherapy promotes cyclical irisin activation, so intermittent treatment is recommended rather than continuous treatment.

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## CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

## SUPPLEMENTARY MATERIALS

Supplementary data including one table and two figures can be found with this article online at <https://doi.org/10.4196/kjpp.2022.26.6.501>.

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