Advances in Integrative Medicine 11 (2024) 2–9

Contents lists available at ScienceDirect

Advances in Integrative Medicine

journal homepage: www.elsevier.com/locate/aimed

A pilot study to evaluate the potential therapeutic effect of hydrogen-water bathing on atopic dermatitis in humans

Ailing Hu [a,b,*], Takuji Yamaguchi [a,b], Masahiro Tabuchi [a], Yasushi Ikarashi [a], Akio Mizushima [b], Hiroyuki Kobayashi [a]

[a] Department of Personalized Kampo Medicine, Juntendo University Graduate School of Medicine, Tokyo, Japan
[b] Department of Palliative Medicine, Juntendo University Graduate School of Medicine, Tokyo, Japan

ARTICLE INFO

Keywords:
Hydrogen-water bathing
Atopic dermatitis
Visual analog scales
Transepidermal water loss
Humans

ABSTRACT

Background: Hydrogen molecules, which have excellent antioxidant and anti-inflammatory effects, are absorbed through the skin and spread hematogenously throughout the body. Hydrogen-water bathing (HWB) is expected to be effective against atopic dermatitis (AD); however, its usefulness remains controversial in humans.
Objective: This study aimed to determine whether HWB has the potential to have a therapeutic effect in a pilot study conducted on six patients with AD.
Methods: AD severity was assessed based on the itching intensity per the visual analog scales (VAS) and the transepidermal water loss (TEWL) values of the lesions, in addition to macroscopic observations.
Results: HWB for eight weeks ameliorated the severity of rashes and increased TEWL levels in the trunk/limb areas that could be completely immersed in the bathwater, resulting in ameliorations in severe itching. The specificity of its therapeutic effect was further investigated in one patient who first underwent HWB for four weeks, discontinued it for two weeks, and resumed it for another four weeks. The rashes on the trunk/limb areas visibly improved after four weeks of HWB but worsened again after it was stopped for two weeks, only to improve again after the resumption of HWB for four weeks. The VAS and TEWL values also showed changes that reflected the skin condition.
Conclusion: These results suggest that HWB may be useful in the treatment of AD. To conclude the effectiveness of HWB for AD, it needs to be supported by randomized controlled trials with larger sample sizes and longer study durations in the future.

1. Introduction

Atopic dermatitis (AD) is a chronically relapsing, pruritic, eczematous skin disorder that occurs alongside allergic inflammation [1–3]. Many patients with AD have an "atopic diathesis," such as medical and/or family histories of developing allergies or a condition associated with the easy production of immunoglobulin E antibodies, which are associated with allergy development [2]. AD is caused by a combination of various environmental factors such as stress, skin conditions, and allergens (including mites, dust, and food). Its causes, clinical manifestations, and exacerbating factors are individually different [2,4,5]. However, AD is generally characterized by skin barrier impairments [6,7], released inflammatory cytokines and chemical messengers [8–10], increased oxidative stress [11–13], and dysfunctional immune systems (such as Th1 and Th2 imbalances) [14,15]. These are closely involved in the pathogenesis and exacerbations of AD [11,16].

The outermost stratum corneum of the normal skin acts as a barrier to excessive skin water loss (transepidermal water loss, TEWL) and allergen (such as bacteria and outside irritants) invasion [17]. However, the barrier function of the skin of patients with AD is compromised, resulting in water loss and dry skin [6]. Therefore, various foreign substances, such as allergens and irritants, easily pass through the gaps in dry skin [18], after which they are detected by immune and/or inflammatory cells, causing allergic inflammation. Various bioactive substances, such as cytokines (interleukin [IL]−4, IL-13, IL-33, IL-25, IL-1β, etc.), chemokines (thymus- and activation-regulating chemokine [TARC], macrophage-derived chemokines, cutaneous T-cell-attracting chemokine, etc.), and chemical mediators (histamine, leukotriene B4,

* Correspondence to: Department of Personalized Kampo Medicine, Juntendo University Graduate School of Medicine, 2–1-1-Hongo, Bunkyo-ku, Tokyo 113-8421, Japan.
E-mail address: ailing@juntendo.ac.jp (A. Hu).

https://doi.org/10.1016/j.aimed.2023.10.003
Received 28 September 2022; Received in revised form 5 October 2023; Accepted 25 October 2023
Available online 3 November 2023

substance P, etc.) are released from various cells (such as inflammatory, immune, and epidermal cells) and form lesions through their complex interaction with each other in inflammatory skin lesions [11,16]. Oxidative stress due to reactive oxygen species (ROS)–antioxidant imbalance and Th1/Th2 immunity or cytokine imbalance are also closely associated with AD development and exacerbation/severity [12–15,19,20].

Also, dry skin often causes hyperesthesia. Sensory nerve fibers in normal skin terminate at the boundary between the epidermis and dermis; however, in dry skin, the fibers proliferate and extend just below the stratum corneum that makes up the skin surface [21]. Various itching substances, such as cytokines, chemokines, and chemical mediators that are released into the skin lesions easily act on stretched nerve fibers; thus, itching is sensitively detected and enhanced. Particularly, barrier dysfunction induces susceptibility to various external stimuli and allergens [18]. Therefore, even a slight stimulus causes itching, promotes scratching behavior, and further destroys the skin barrier, forming a vicious circle called a negative spiral [16,22].

Hydrogen molecules (H_2) have excellent antioxidant and anti-inflammatory actions, as well as antiapoptosis, antiallergy, and energy metabolism activation [23–26]. The biological safety of hydrogen water was confirmed in mutagenicity tests using several bacteria, genotoxicity tests using Chinese hamster lung fibroblast cells, and subchronic oral toxicity tests using rats [27]. Hydrogen was also confirmed to be non-cytotoxic and safe in humans, even at high concentrations, in deep-sea diving studies using hydrogen-containing breathing gas [28,29] and an intravenous hydrogen administration study in patients with acute cerebral ischemia [30]. Therefore, its medical application is expected as a new strategy for the prevention and treatment of many diseases, such as diabetes, arteriosclerosis, cognitive impairment, cancer, and allergies [23–26,31–34].

Among various beneficial effects, drinking hydrogen water abolishes immediate-type allergic reactions through radical scavenging activity in mice [35]. Regarding AD, drinking hydrogen water ameliorated the *Dermatophagoides farina* allergen-induced [31] and 2,4-dinitrochlorobenzene-induced AD [36] in AD model NC/Nga mice. These effects were associated with antioxidant stress, selective ROS removal, inflammatory cytokine level reduction, immunoglobulin E antibody suppression, and cytokine or immune imbalance amelioration [31,36]. We previously demonstrated that drinking hydrogen water abated the severity of AD-like skin lesions such as erythema/hemorrhage, edema, erosion/excoriation, and dryness, which was associated with TEWL suppression, mast cell infiltration, and proinflammatory cytokine (such as IL-1β and IL-33) secretion in skin lesions, and serum TARC suppression in NC/Nga mice [37]. Additionally, hydrogen water intake via tube feeding has resulted in reduced wound size and early recovery for severely hospitalized elderly patients with pressure ulcers [38]. These pieces of evidence suggest the effectiveness of hydrogen water consumption in the treatment of AD.

Hydrogen-water bathing (HWB) is another method of efficiently bringing hydrogen into the body (in addition to drinking). Hydrogen easily passes through the skin and distributes throughout the body via circulation [24,25]. Thus, HWB, which directly takes in hydrogen through the skin, seems more effective for AD treatment. In a previous study, HWB inhibited ultraviolet B radiation-induced skin injury, increased ROS, and increased the activity of inflammatory cytokines (including IL-1β, IL-6, tumor necrosis factor-α, and interferon-γ) in hairless mice [39]. In healthy humans, HWB not only increases the skin's elasticity and water content [40] but also cleanses pores that are clogged with keratin plugs and promotes blood flow in capillaries [41]. Furthermore, HWB significantly improved the wrinkles on the back of the neck in healthy female volunteers (31.5 ± 11.4 years), a finding that is associated with ROS scavenging and type I collagen synthesis promotion in the dermis [42]. A case study reported that HWB improved extensive skin blotches on the left lower leg in a 41-year-old female patient as well as back and chest pimples and dry skin that were present for years in a 48-year-old female patient [43]. In another study, HWB abated the severity of chronic inflammatory skin diseases, psoriasis, and parapsoriasis en plaques as assessed by the psoriasis region severity index score and the itching score using the visual analog scale (VAS) [44]. These findings suggest that HWB could be effective in treating AD. However, to our knowledge, no studies have scientifically investigated the therapeutic effect of HWB on humans with AD.

Therefore, the present study aimed to determine whether HWB has the potential to have a therapeutic effect in a pilot study including six patients with AD based on the itching (assessed using the VAS) and TEWL values of the lesions and macroscopic observation to assess AD severity.

2. Material and methods

2.1. Participants and ethics statement

This study included six patients with AD (one male and five females, mean age: 39.2 ± 3.40 years) and seven healthy adult volunteers (two males and five females, mean age: 31.4 ± 2.9 years) as controls. Informed consent was obtained from all participants. All procedures performed in the present study complied with the Helsinki Declaration and the Ethical Guidelines for Medical and Health Research Involving Human Subjects. The study was approved by the Ethics Committee of Medical Corp Koyokai (KEC-2017–01).

2.2. Experimental designs

2.2.1. Severity assessment of AD in patients with the condition compared to healthy subjects

The severity of AD in patients with the condition ($n = 6$) was assessed by gross observation (photographing), the intensity of itching per self-assessed VAS, and the TEWL value in skin lesions. These assessments were performed at the first visit to the Kampo outpatient department of Juntendo Hospital (Tokyo, Japan). Patient data were compared to those of healthy subjects ($n = 7$). The nighttime VAS evaluation (before bedtime) was conducted at each person's home.

2.2.2. HWB effects

2.2.2.1. Evaluation of HWB for eight weeks. To assess the therapeutic effectiveness of HWB on AD, five out of six patients with the condition bathed at home in hydrogen water (at a temperature of 38 °C—40 °C) for 30 min every afternoon for eight weeks (56 days). All subjects self-assessed the degree of itching two times a day; i.e., in the daytime and in the nighttime (before bedtime), using the VAS during the experimental period. We aggregated these data weekly to calculate each average value in the daytime and the nighttime per week. Photographs were taken and TEWL measurements of the dermatitis areas in all patients were performed between 15:00 and 17:00 in the Kampo outpatient department of Juntendo Hospital at the 0th (pre-data), 4th, and 8th weeks of the experiment.

2.2.2.2. Effects of stopping and resuming HWB. Only one of six patients was enrolled to assess the specificity and persistence of HWB effects on AD. The subject first performed HWB at home for four weeks, discontinued it for two weeks (during which, normal bathing was performed instead of HWB), and resumed for four weeks. The itching intensity was self-assessed twice daily in the daytime and nighttime (before bedtime) using the VAS during the ten-week (seventy-day) experiment. We aggregated these data weekly to calculate each average value in the daytime and nighttime per week. Photographs and TEWL measurements of skin lesions were performed between 15:00 and 17:00 in the Kampo outpatient department of Juntendo Hospital at 0 (pre-data), 4, 6, 8, and 10 weeks of the experiment.

2.3. HWB preparation using a hydrogen generator

A pot-type hydrogen generator (Hydrogen SPA® H-Pot, device size; width 140 mm × depth 140 mm × height 190 mm, Gohda water treatment technology Co. Inc., Tokyo, Japan) was used to generate hydrogen in a bathtub containing warm water. Hydrogen generation in this device is done using the "metal magnesium reaction method" in which metallic magnesium (Mg) reacts with water to yield hydrogen as shown by the following reaction: $Mg + 2\,H_2O \rightarrow Mg(OH)_2 + H_2$. Briefly, after removing the large perforated upper lid of the pot-type device, four magnesium cores (core size: width 73 mm × depth 35 mm × height 70 mm, magnesium purity >99.9%) were set on the bottom of the device. After closing the upper lid, approximately 4 g of citric acid was added as a catalyst (activator) for hydrogen generation through a hole in the upper lid, and warm water (approximately 40 °C) was poured. The device was left for 2–3 min to promote hydrogen production. After confirming that sufficient hydrogen was generated, it was submerged in the bathtub containing the bathwater (at a temperature of 38 °C—40 °C). The Mg core in the device continued to generate hydrogen in the bathwater. After the subject bathed for 30 min, the device was removed from the bathwater, dried naturally, and kept until the next use.

The hydrogen concentration, which was measured using the ENH-2000 Portable Dissolved Hydrogen Meter (Sato Shouji Inc. Kanagawa, Japan), was 294 ppb in 320 L of warm water (at a temperature of 38–40 °C).

2.4. Itching assessment using VAS

The VAS is an internationally widely used scale for quantifying subjective clinical manifestations (symptoms, such as itching), which consists of a 100-mm-long line and one question [45,46]. The left point (0 mm) represents "no itch" and the right endpoint (100 mm) represents the "worst imaginable itch." The patient marked the degree of pruritus felt on the line. The intensity of itching was quantified as a VAS score by measuring the distance from the 0-mm point.

2.5. TEWL assessment

Before measuring TEWL, subjects acclimatized for 30 min in a room at room temperature (24 °C—25 °C) and 50%—55% humidity. Meanwhile, the subjects marked their itchy areas (dermatitis areas) on the illustration sheet (Fig. 1) showing the front and back of the whole body. The itchy sites were then examined by a medical doctor, and TEWL levels in the areas were measured using the TM300-Tewameter probe connected to an MDD4 multi-display device (Integral Co., Tokyo, Japan). Additionally, photographs of lesions were taken as needed. The location and number of TEWL measurements varied from person to person because the sites of onset of lesions varied too. Therefore, the measured values were finally assessed by dividing them into two areas: the "head/neck," which included the ① forehead, ② cheeks, ③ neck, and ④ shoulders, representing areas that were insufficiently immersed in the bathwater, and the "trunk/limb," which included the ⑤ chest, ⑥ abdomen, ⑦ and ⑧ back, including waist, and ⑨–⑬ limbs (arms and legs), representing areas that were sufficiently immersed in the bathwater. The TEWL values for both areas in the AD group were expressed as the average of the measured values at the observed lesion sites in each of the six patients with AD.

2.6. Statistical analysis

A comparative study of itching severity in patients with AD and healthy subjects was expressed by the VAS and TEWL data as the mean ± standard error of the mean (SEM) for subjects in each group. Statistical significance was assessed using Dunnett's multiple comparison test after the unpaired nonparametric Kruskal–Wallis test.

The VAS and TEWL data were expressed as the mean ± SEM of five patients with AD in the eight-week HWB evaluation study. Statistical significance was assessed using Dunnett's multiple comparison test after Friedman's paired nonparametric test.

The TEWL data were expressed as the mean ± SEM of 20 measurement sites in a single patient with AD in a ten-week evaluation study consisting of HWB, discontinuation, and re-bathing. Statistical significance was assessed using Dunnett's multiple comparison test after Friedman's paired nonparametric test. Statistical analysis of VAS data was not conducted because there was only one subject.

The threshold for statistical significance in this study was set at $P < 0.05$.

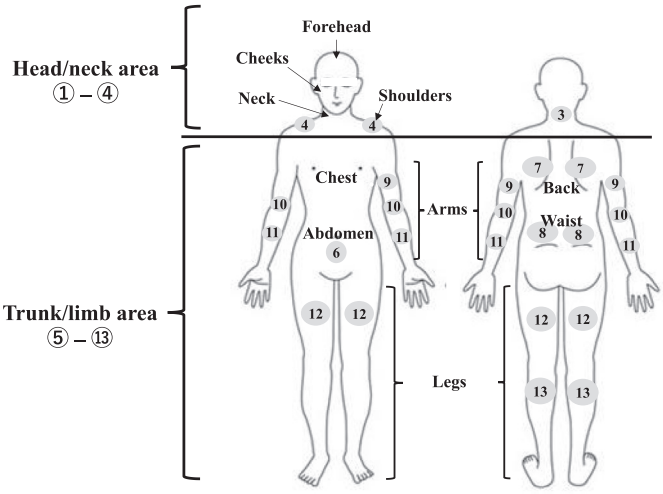

Fig. 1. Illustration sheet showing the front and back of the whole body and transepidermal water loss (TEWL) measurement sites. TEWL levels on the ① forehead, ② cheeks, ③ neck, ④ shoulders, ⑤ chest, ⑥ abdomen, ⑦ and ⑧ back including waist, and ⑨–⑬ limbs (arms and legs) were measured using the TM300-Tewameter probe connected to an MDD4 multi-display device. The measured values were finally averaged by dividing them into two areas, including the "head/neck" ①–④ (which was insufficiently immersed in bathwater) and the "trunk/limb" ⑤–⑬ (which was sufficiently immersed in bathwater).

3. Results

3.1. The severity of AD in patients with the condition compared to healthy control subjects

Fig. 2A shows skin conditions of the foreheads, necks, arms, backs, and legs of patients with AD and those of healthy control subjects. Rashes (eczema), dry skin, and scabs were observed on the foreheads, necks, arms, backs, and legs of patients with AD compared to the control subjects.

Fig. 2B shows the daytime and nighttime itching intensity as self-assessed by patients with AD and control subjects using the VAS. Daytime and nighttime VAS scores in patients with AD significantly increased, indicating that both itching intensities in patients with AD were stronger those in control subjects. The intensity of pruritus in patients with AD did not differ significantly between the daytime and the nighttime; however, nighttime itching was stronger than daytime itching.

Fig. 2C shows the TEWL values in patients with AD and control subjects. The TEWL values in the head/neck and trunk/limb areas of patients with AD significantly increased, indicating that their skin lesion areas were significantly drier than the corresponding areas of the control subjects.

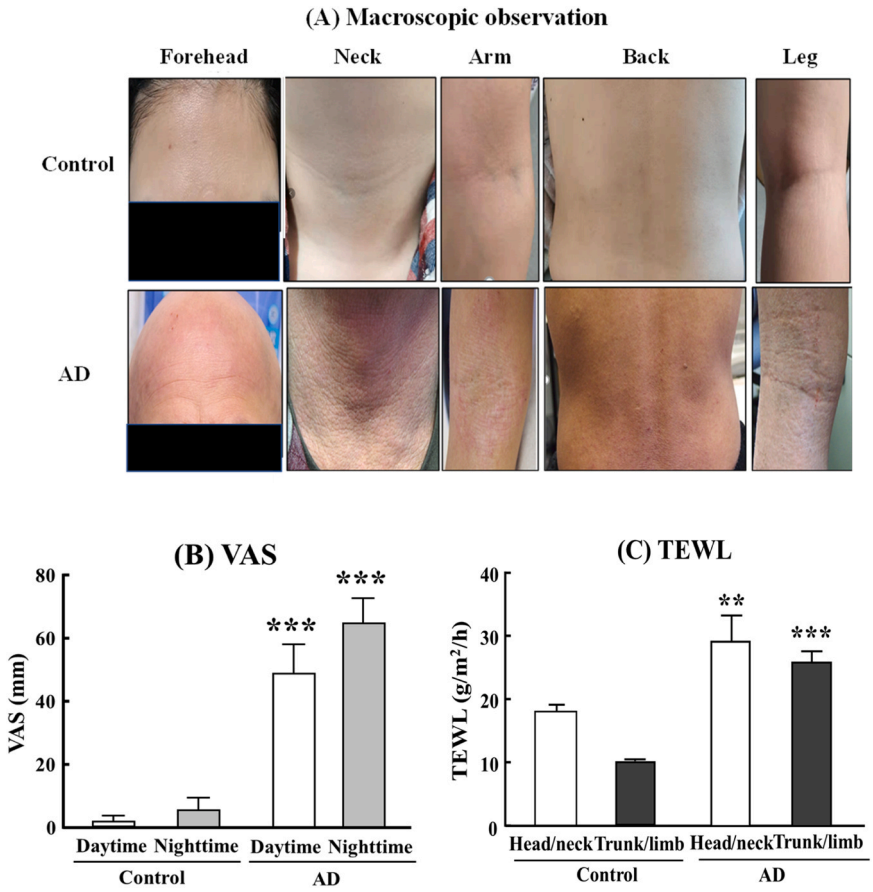

Fig. 2. The severity of atopic dermatitis (AD) in patients compared to that in healthy control subjects. The severity of AD in patients was assessed by (A) macroscopic observation, (B) itching intensity evaluation using the visual analog scale (VAS), and (C) TEWL values of skin lesions. (A) The photographs show typical skin conditions on the forehead, neck, arms, back, and legs in patients with AD compared to those in control subjects. (B) All subjects performed self-assessments of the degree of itching twice daily, in the daytime and nighttime (before bedtime), using the VAS. (C) TEWL values in the head/neck and trunk/limb areas of patients with AD and the corresponding areas of healthy controls were measured using the TM300-Tewameter probe connected to an MDD4 multi-display device. (B) and (C) VAS and TEWL data are expressed as the mean ± SEM of seven subjects in the control group and six subjects in the AD group. Statistical significance was assessed using Dunnett's multiple comparison test after the unpaired nonparametric Kruskal–Wallis test. $^{**}P < 0.01$ and $^{***}P < 0.001$ vs. corresponding data from control subjects.

3.2. Ameliorating effect of HWB on dermatitis

Fig. 3 shows skin lesion changes and the VAS and TEWL values in patients with AD who underwent HWB for eight weeks.

Neck (throat) rashes, which were insufficiently immersed in bathwater, showed a tendency to slightly decrease with an 8-week HWB; however, there was no significant improvement. Meanwhile, trunk/limb area rashes, which were sufficiently immersed in bathwater, significantly improved by the end of the eight-week HWB period (Fig. 3A).

The VAS score before bathing (week 0) increased more in the nighttime than in the daytime; however, there was no significant difference between the two, and the VAS levels in both time zones gradually decreased during the eight-week HWB period. Significant reductions in the daytime and nighttime VAS levels were observed from seven and eight weeks of bathing, respectively (Fig. 3B).

Fig. 3C and D show TEWL value changes in the head/neck and trunk/limb areas after HWB. Head/neck rashes were slightly improved after bathing as aforementioned; however, the TEWL values did not differ significantly after the eight-week HWB period (Fig. 3C). Meanwhile, the TEWL values in the trunk/limb area, which showed an improved eruption, were significantly reduced by the eight-week HWB at 4–8 weeks of bathing (Fig. 3D). This result meant that exposure to hydrogen water increased the moisturizing power of skin lesions and improved dry skin.

3.3. Specific therapeutic effects of HWB on AD symptoms

The specific therapeutic effect of HWB on AD symptoms was investigated in one patient who suffered from dermatitis with marked rashes (eczema) in the back area. The subject first performed HWB for four weeks, discontinued it for two weeks, and then restarted for four weeks. Fig. 4A shows skin lesion changes on the back area during a series of procedures, including HWB interruption and resumption. Back area rashes were visibly ameliorated by a four-week HWB (fourth-week photo). However, the ameliorated area was exacerbated by interrupting HWB for two weeks (sixth-week photo: relapse of eczema). The relapsed rash was resolved by the re-commencement of HWB for four weeks (tenth-week photo).

The VAS and TEWL values in the lesion area showed changes that reflected the skin condition. Particularly, VAS scores, which were high during the daytime and nighttime at week 0, decreased after four weeks of HWB, increased again upon discontinuation for two weeks, and decreased after restarting HWB for four weeks (Fig. 4B). The TEWL value, which was high at week 0, decreased after four weeks of HWB, increased again upon discontinuation for two weeks, and decreased again after restarting the HWB for four weeks (Fig. 4C).

4. Discussion

This was a pilot study to determine whether HWB has the potential to

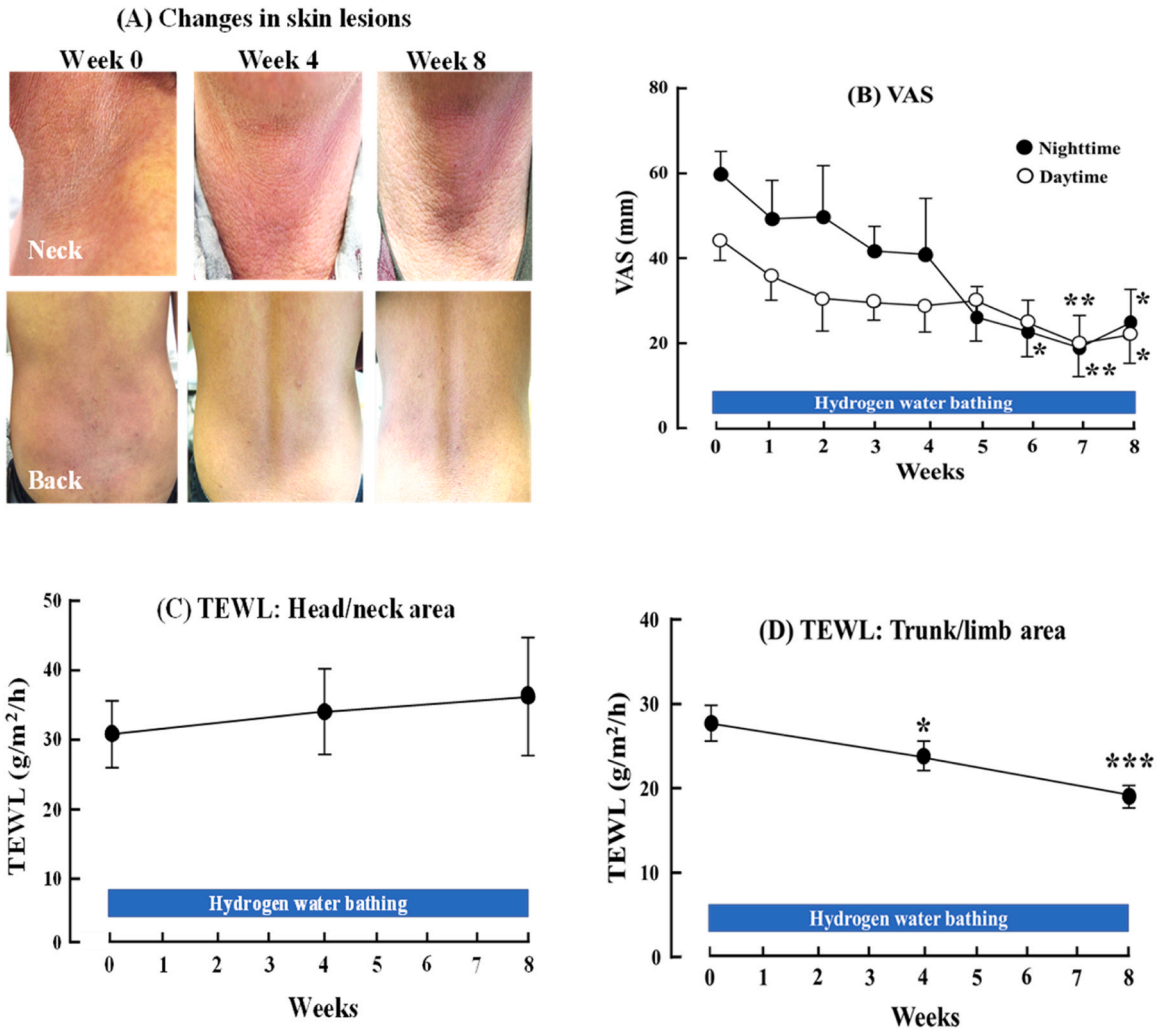

Fig. 3. Skin lesion changes and VAS and TEWL values in patients with AD who underwent hydrogen-water bathing for eight weeks. (A) The photographs show typical skin lesion changes on the neck and back areas before (the 0th week) and the 4th and 8th weeks of the bathing. (B) Patients with AD performed self-assessments of the degree of itching twice daily, in the daytime and nighttime, using the VAS. (C and D) TEWL values in the head/neck and trunk/limb areas of patients with AD were measured using the TM300-Tewameter probe connected to an MDD4 multi-display device. (B, C, and D) VAS and TEWL data are expressed as the mean ± SEM of five patients. Statistical significance was assessed using Dunnett's multiple comparison test after the paired nonparametric Friedman's test. * $P < 0.05$, ** $P < 0.01$, and *** $P < 0.001$ vs. data from control subjects (week 0).

treat AD. Patients with AD in this study had marked rashes with severe itching and dry skin on various skin areas. The severity of pruritus and dry skin in patients was supported by significant increments in VAS scores and TEWL levels (Fig. 2). These symptoms in the trunk/limb areas of AD patients were significantly improved by eight weeks of HWB (Fig. 3). The specificity of HWB for AD was further investigated in one patient who suffered from dermatitis with marked rashes (eczema) in the trunk/limb areas (Fig. 4). The rashes on the trunk/limb areas significantly improved after four weeks of HWB but worsened upon discontinuation for two weeks and recovered again upon HWB resumption for four weeks. The VAS and TEWL values also showed changes that reflected the skin condition. These results suggest that HWB may be involved in the alleviation of AD symptoms but also highlight the fact that HWB discontinuation may cause symptom recurrence.

Various methods, such as drinking hydrogen water, inhaling hydrogen gas, injecting hydrogen-dissolving physiological saline, and HWB, have been introduced to supply the body with hydrogen molecules [24,25]. Since hydrogen easily penetrates the skin and is distributed throughout the body by the circulation of blood [24,25], HWB, which allows hydrogen to act directly on the skin, may be more effective in treating AD. Actually, HWB has been reported to improve skin conditions such as skin elasticity [40], skin capillary blood flow [40], wrinkles [38], skin blotches, pimples, and dry skin [43,44]. The alleviating effect of HWB on skin conditions may be stronger (due to the direct effect of hydrogen penetrating the skin) than that of hydrogen ingested and absorbed/distributed to body tissues. This is because, as already mentioned, the skin condition in the trunk/limb areas of patients with AD was improved by HWB for eight weeks but those in the head/neck area were hardly improved (Fig. 3). The difference in the effectiveness of HWB on areas affected by atopic dermatitis may be due to the fact that the trunk/limb areas are sufficiently immersed in the bathtub for a long time, whereas the head/neck areas are immersed for shorter periods.

This study had several limitations. First, considering the study design (including the small number of participants and the short study duration), the effectiveness of HMB for AD should be evaluated as a possible effect rather than a definitive one. Therefore, the effectiveness of HWB needs to be supported by randomized controlled trials with larger sample sizes and longer study periods to conclude its effectiveness for AD. Second, the recurrence of AD when the HWB is interrupted and the method of applying hydrogen water to areas where continuous immersion in bathtub water is difficult. Regarding the former, we think that a

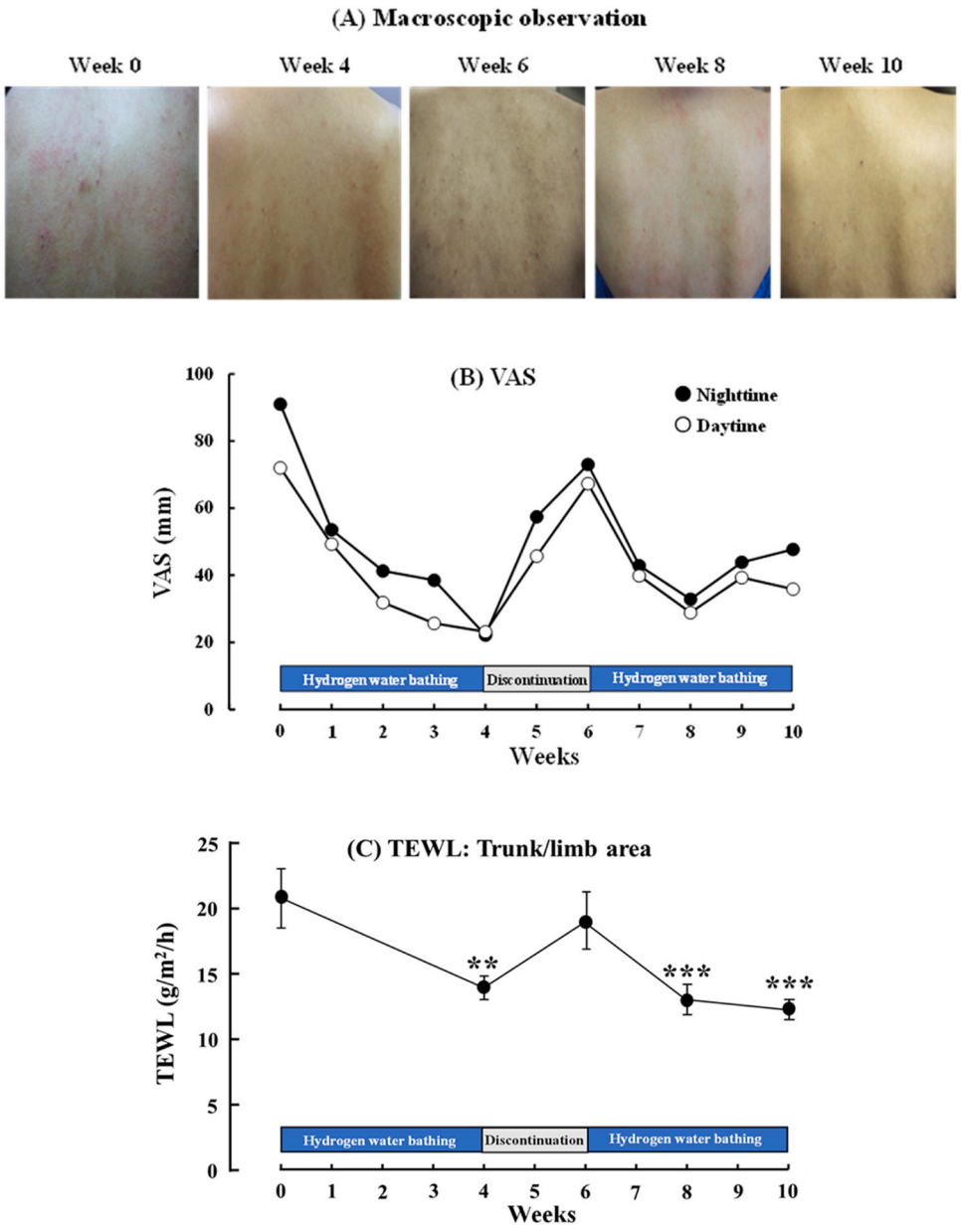

Fig. 4. The specific therapeutic effect of hydrogen water bathing on AD symptoms. One patient with AD first performed hydrogen-water bathing for four weeks, discontinued it for two weeks, and then restarted it for four weeks. (A) Changes in skin lesions on the back area were observed during a series of procedures. (B) Changes in itching index VAS scores in the daytime and nighttime during this study. (C) Changes in dry skin index TEWL values as measured using the TM300-Tewameter probe connected to an MDD4 multi-display device. Data are expressed as the mean ± SEM of 20 measurement sites in the skin lesion area of one patient with AD. Statistical significance was assessed using Dunnett's multiple comparison test after the paired nonparametric Friedman's test.

habitual HWB is important. In the future, it will be necessary to investigate recurrence in patients who have undergone habitual HWB. For the latter, applying a face or neck pack method in which cotton or a sheet moistened with hydrogen water is brought into close contact with the skin of the face or neck, making it possible for hydrogen to penetrate the skin. In the future, investigating the effect of combining HWB and face/neck packs in patients with AD will be necessary. Additionally, drinking hydrogen water has been reported to improve the clinical manifestations of AD in several AD animal models [31,36,37]. This suggests that drinking hydrogen water may also be effective against AD in humans. Therefore, although future clinical studies are required for confirmation, the combination of HWB and hydrogen drinking water may be useful as a solution to this problem.

5. Conclusion

This study suggests that HWB may be useful in the treatment of AD. In the future, randomized controlled trials with larger sample sizes and longer periods are needed to draw solid conclusions regarding the effectiveness of HWB for AD.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethical Statement

Informed consent was obtained from all participants. All procedures

performed in the present study complied with the Helsinki Declaration and the Ethical Guidelines for Medical and Health Research Involving Human Subjects. The study was approved by the Ethics Committee of Medical Corp Koyokai (KEC-2017–01).

CRediT authorship contribution statement

Hu Ailing: Conceptualization, Investigation, Methodology, Writing – original draft preparation. **Yamaguchi Takuji**: Conceptualization, Investigation, Methodology, Resources. **Tabuchi Masahiro**: Conceptualization, Formal analysis, Data curation, Visualization. **Ikarashi Yasushi**: Conceptualization, Writing – review & editing. **Mizushima Akio**: Writing – review & editing. **Kobayashi Hiroyuki**: Conceptualization, Resources, Supervision, Project administration.

Declaration of Competing Interest

None.

Acknowledgements

The authors thank Enago (www.enago.jp) for the English language review.

References

[1] A.B. Kay, Allergy and allergic diseases. First of two parts, N. Engl. J. Med 344 (2001) 30–37, https://doi.org/10.1056/NEJM200101043440106.
[2] I. Katayama, Y. Kohno, K. Akiyama, Z. Ikezawa, N. Kondo, K. Tamaki, O. Kouro, Japanese Society of Allergology, Japanese guideline for atopic dermatitis, Allergol. Int. 60 (2011) 205–220, https://doi.org/10.2332/allergolint.11-RAI-0333.
[3] N. Novak, New insights into the mechanism and management of allergic diseases: atopic dermatitis, Allergy 64 (2009) 265–275, https://doi.org/10.1111/j.1398-9995.2008.01922.x.
[4] K.C. Madison, Barrier function of the skin: "la raison d'être" of the epidermis, J. Invest. Dermatol. 121 (2003) 231–241, https://doi.org/10.1046/j.1523-1747.2003.12359.x.
[5] K.M. Sanders, T. Akiyama, The vicious cycle of itch and anxiety, Neurosci. Biobehav. Rev. 87 (2018) 17–26, https://doi.org/10.1016/j.neubiorev.2018.01.009.
[6] G. Imokawa, A. Abe, K. Jin, Y. Higaki, M. Kawashima, A. Hidano, Decreased level of ceramides in stratum corneum of atopic dermatitis: an etiologic factor in atopic dry skin? J. Invest. Dermatol. 96 (1991) 523–526, https://doi.org/10.1111/1523-1747.ep12470233.
[7] T. Yoshida, L.A. Beck, A.D. De Benedetto, Skin barrier defects in atopic dermatitis: from old idea to new opportunity, Allergol. Int. 71 (2022) 3–13, https://doi.org/10.1016/j.alit.2021.11.006.
[8] E.B. Brandt, U. Sivaprasad, Th2 cytokines and atopic dermatitis, J. Clin. Cell. Immunol. 2 (2011) 110, https://doi.org/10.4172/2155-9899.1000110.
[9] T. Okabe, M. Hide, O. Koro, N. Nimi, S. Yamamoto, The release of leukotriene B4 from human skin in response to substance P: evidence for the functional heterogeneity of human skin mast cells among individuals, Clin. Exp. Immunol. 124 (2001) 150–156, https://doi.org/10.1046/j.1365-2249.2001.01486.x.
[10] H. Siiskonen, I. Harvima, Mast cells and sensory nerves contribute to neurogenic inflammation and pruritus in chronic skin inflammation, Front. Cell. Neurosci. 13 (2019) 422, https://doi.org/10.3389/fncel.2019.00422.
[11] S. Briganti, M. Picardo, Antioxidant activity, lipid peroxidation and skin diseases. What's new, J. Eur. Acad. Dermatol. Venereol. 17 (2003) 663–669, https://doi.org/10.1046/j.1468-3083.2003.00751.x.
[12] N. Sivaranjani, S.V. Rao, G. Rajeev, Role of reactive oxygen species and antioxidants in atopic dermatitis, J. Clin. Diagn. Res 7 (2013) 2683–2685, https://doi.org/10.7860/JCDR/2013/6635.3732.
[13] H. Tsukahara, R. Shibata, Y. Ohshima, Y. Todoroki, S. Sato, N. Ohta, M. Hiraoka, A. Yoshida, S. Nishima, M. Mayumi, Oxidative stress and altered antioxidant defenses in children with acute exacerbation of atopic dermatitis, Life Sci. 72 (2003) 2509–2516, https://doi.org/10.1016/S0024-3205(03)00145-0.
[14] A. Grassegger, R. Höpfl, Significance of the cytokine interferon gamma in clinical dermatology, Clin. Exp. Dermatol. 29 (2004) 584–588, https://doi.org/10.1111/j.1365-2230.2004.01652.x.
[15] K. Hattori, M. Nishikawa, K. Watcharanurak, A. Ikoma, K. Kabashima, H. Toyota, Y. Takahashi, R. Takahashi, Y. Watanabe, Y. Takakura, Sustained exogenous expression of therapeutic levels of IFN-gamma ameliorates atopic dermatitis in NC/Nga mice via Th1 polarization, J. Immunol. 184 (2010) 2729–2735, https://doi.org/10.4049/jimmunol.0900215.
[16] D.Y. Leung, M. Boguniewicz, M.D. Howell, I. Nomura, Q.A. Hamid, New insights into atopic dermatitis, J. Clin. Invest 113 (2004) 651–657, https://doi.org/10.1172/JCI21060.
[17] P.M. Elias, Skin barrier function, Curr. Allergy Asthma Rep. 8 (2008) 299–305, https://doi.org/10.1007/s11882-008-0048-0.
[18] J.A. Bouwstra, M. Ponec, The skin barrier in healthy and diseased state, Biochim. Biophys. Acta 2006 (1758) 2080–2095, https://doi.org/10.1016/j.bbamem.2006.06.021.
[19] P.M. Brunner, E. Guttman-Yassky, D.Y.J. Leung, The immunology of atopic dermatitis and its reversibility with broad-spectrum and targeted therapies, J. Allergy Clin. Immunol. 139 (2017) S65–S76, https://doi.org/10.1016/j.jaci.2017.01.011.
[20] G. Yang, J.K. Seok, H.C. Kang, Y.Y. Cho, H.S. Lee, J.Y. Lee, Skin barrier abnormalities and immune dysfunction in atopic dermatitis, Int. J. Mol. Sci. 21 (2020) 2867, https://doi.org/10.3390/ijms21082867.
[21] M. Tominaga, K. Takamori, Itch and nerve fibers with special reference to atopic dermatitis: therapeutic implications, J. Dermatol. 41 (2014) 205–212, https://doi.org/10.1111/1346-8138.12317.
[22] G. Yosipovitch, L. Misery, E. Proksch, M. Metz, S. Ständer, M. Schmelz, Skin barrier damage and itch: review of mechanisms, topical management and future directions, Acta Derm. Venereol. 99 (2019) 1201–1209, https://doi.org/10.2340/00015555-3296.
[23] I. Ohsawa, M. Ishikawa, K. Takahashi, M. Watanabe, K. Nishimaki, K. Yamagata, K. Katsura, Y. Katayama, S. Asoh, S. Ohta, Hydrogen acts as a therapeutic antioxidant by selectively reducing cytotoxic oxygen radicals, Nat. Med. 13 (2007) 688–694, https://doi.org/10.1038/nm1577.
[24] S. Ohta, Recent progress toward hydrogen medicine: potential of molecular hydrogen for preventive and therapeutic applications, Curr. Pharm. Des. 17 (2011) 2241–2252, https://doi.org/10.2174/138161211797052664.
[25] S. Ohta, Initiation, development and potential of hydrogen medicine: toward therapeutic and preventive applications of molecular hydrogen against a variety of diseases, Seikagaku 87 (2015) 82–90, https://doi.org/10.14952/SEIKAGAKU.2015.870082/index.html.
[26] M. Watanabe, Y. Yurugi, I. Arisue, H. Fujita, M. Izuta, M. Nishii, K. Tsukiyama, K. Watanabe, Reactive oxygen species and hydrogen therapy, J. Allied Health Sci. 11 (2020) 160–174, https://doi.org/10.15563/jalliedhealthsci.11.160.
[27] Y. Saitoh, Y. Harata, F. Mizuhashi, M. Nakajima, N. Miwa, Biological safety of neutral-pH hydrogen-enriched electrolyzed water upon mutagenicity, genotoxicity and subchronic oral toxicity, Toxicol. Ind. Health 26 (2010) 203–216, https://doi.org/10.1177/0748233710362989.
[28] J.H. Abraini, M.C. Gardette-Chauffour, E. Martinez, J.C. Rostain, C. Lemaire, Psychophysiological reactions in humans during an open sea dive to 500 m with a hydrogen-helium-oxygen mixture, J. Appl. Physiol. 76 (1994) 1113–1118, https://doi.org/10.1152/jappl.1994.76.3.1113.
[29] P. Fontanari, M. Badier, C. Guillot, C. Tomei, H. Burnet, B. Gardette, Y. Jammes, Changes in maximal performance of inspiratory and skeletal muscles during and after the 7.1-MPa Hydra 10 record human dive, Eur. J. Appl. Physiol. 81 (2000) 325–328, https://doi.org/10.1007/s004210050050.
[30] K. Nagatani, H. Nawashiro, S. Takeuchi, S. Tomura, N. Otani, H. Osada, K. Wada, H. Katoh, N. Tsuzuki, K. Mori, Safety of intravenous administration of hydrogen-enriched fluid in patients with acute cerebral ischemia: initial clinical studies, Med. Gas. Res. 3 (2013) 13, https://doi.org/10.1186/2045-9912-3-13.
[31] R.M. Ignacio, H.S. Kwak, Y.U. Yun, M.E. Sajo, Y.S. Yoon, C.S. Kim, S.K. Kim, K. J. Lee, The drinking effect of hydrogen water on atopic dermatitis induced by dermatophagoides farinae allergen in NC/Nga mice, Evid. Based Complement. Altern. Med. 2013 (2013), 538673, https://doi.org/10.1155/2013/538673.
[32] C. Liu, J. Cui, Q. Sun, J. Cai, Hydrogen therapy may be an effective and specific novel treatment for acute radiation syndrome, Med. Hypo 74 (2009) 145–146, https://doi.org/10.1016/j.mehy.2009.07.017.
[33] L. Qian, J. Shen, Y. Chuai, J. Cai, Hydrogen as a new class of radioprotective agent, Int. J. Biol. Sci. 9 (2013) 887–894, https://doi.org/10.7150/ijbs.7220.
[34] Y. Yang, Y. Zhu, X. Xi, Anti-inflammatory and antitumor action of hydrogen via reactive oxygen species, Oncol. Lett. 16 (2018) 2771–2776, https://doi.org/10.3892/ol.2018.9023.
[35] T. Itoh, Y. Fujita, M. Ito, A. Masuda, K. Ohno, M. Ichihara, T. Kojima, Y. Nozawa, M. Ito, Molecular hydrogen suppresses FcepsilonRI-mediated signal transduction and prevents degranulation of mast cells, Biochem. Biophys. Res. Commun. 389 (2009) 651–656, https://doi.org/10.1016/j.bbrc.2009.09.047.
[36] Y.S. Yoon, M.E. Sajo, R.M. Ignacio, S.K. Kim, C.S. Kim, K.J. Lee, Positive effects of hydrogen water on 2,4-dinitrochlorobenzene-induced atopic dermatitis in NC/Nga mice, Biol. Pharm. Bull. 37 (2014) 1480–1485, https://doi.org/10.1248/bpb.b14-00220.
[37] T. Kajisa, T. Yamaguchi, A. Hu, N. Suetake, H. Kobayashi, Hydrogen water ameliorates the severity of atopic dermatitis-like lesions and decreases interleukin-1β, interleukin-33, and mast cell infiltrationin NC/Nga mice, Saudi Med. J. 38 (2017) 928–933, https://doi.org/10.15537/smj.2017.9.20807.
[38] Q. Li, S. Kato, D. Matsuoka, H. Tanaka, N. Miwa, Hydrogen water intake via tube-feeding for patients with pressure ulcer and its reconstructive effects on normal human skin cells in vitro, Med. Gas. Res. 3 (2013) 20, https://doi.org/10.1186/2045-9912-3-20.
[39] R.M. Ignacio, Y.S. Yoon, M.E.J. Sajo, C.S. Kim, D.H. Kim, S.K. Kim, K. Lee, The balneotherapy effect of hydrogen reduced water on UVB-mediated skin injury in hairless mice, Mol. Cell. Toxicol. 9 (2013) 15–21, https://doi.org/10.1007/s13273-013-0003-6.
[40] Y. Kurita, K. Umeda, S. Ikeda, O. Urushibata, S. Okouchi, Effects of magnesium hydride as a reductive bath additive on the skin, J. Hot Spring Sci. 63 (2014) 317–327. ⟨www.j-hss.org/journal/back_number/vol63_pdf/vol63no4_317_327.pdf⟩.

[41] Y. Tanaka, Y. Saitoh, N. Miwa, Electrolytically generated hydrogen warm water cleanses the keratin-plug-clogged hair-pores and promotes the capillary blood-streams, more markedly than normal warm water does, Med. Gas. Res. 8 (2018) 12–18, https://doi.org/10.4103/2045-9912.229598.

[42] S. Kato, Y. Saitoh, K. Iwai, N. Miwa, Hydrogen-rich electrolyzed warm water represses wrinkle formation against UVA ray together with type-I collagen production and oxidative-stress diminishment in fibroblasts and cell-injury prevention in keratinocytes, J. Photochem. Photobiol. B 106 (2012) 24–33, https://doi.org/10.1016/j.jphotobiol.2011.09.006.

[43] R. Asada, Y. Saitoh, N. Miwa, Effects of hydrogen-rich water bath on visceral fat and skin blotch, with boiling-resistant hydrogen bubbles, Med. Gas. Res. 9 (2019) 68–73, https://doi.org/10.4103/2045-9912.260647.

[44] Q. Zhu, Y. Wu, Y. Li, Z. Chen, L. Wang, H. Xiong, E. Dai, J. Wu, B. Fan, L. Ping, X. Luo, Positive effects of hydrogen-water bathing in patients of psoriasis and parapsoriasis en plaques, Sci. Rep. 8 (2018) 8051, https://doi.org/10.1038/s41598-018-26388-3.

[45] A. Reich, C. Riepe, Z. Anastasiadou, K. Mędrek, M. Augustin, J.C. Szepietowski, S. Ständer, Itch assessment with visual analogue scale and numerical rating scale: determination of minimal clinically important difference in chronic itch, Acta Derm. Venereol. 96 (2016) 978–980, https://doi.org/10.2340/00015555-2433.

[46] A. Reich, E. Chatzigeorkidis, C. Zeidler, N. Osada, M. Furue, K. Takamori, T. Ebata, M. Augustin, J.C. Szepietowski, S. Ständer, Tailoring the cut-off values of the visual analogue scale and numeric rating scale in itch assessment, Acta Derm. Venereol. 97 (2017) 759–760, https://doi.org/10.2340/00015555-2642.