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The application of repeated whole-body cryotherapy in atopic dermatitis and its impact on *Staphylococcus aureus* colonization — pilot study

Magdalena Kępińska-Szyszkowska[1], Anna Misiorek[1], Monika Kapińska-Mrowiecka[2], Karolina Reiprich[2]

[1]*Institute of Applied Sciences, University of Physical Education in Krakow, Kraków, Poland*
[2]*Dermatology Ward, Stefan Zeromski Hospital in Krakow, Kraków, Poland*

ABSTRACT

Introduction: *Staphylococcus aureus* can directly penetrate the *stratum corneum* and epidermis, which explains why this microorganism can disrupt the immune homeostasis of the skin and potentially influence skin diseases. Whole-body cryotherapy (W-BC) is one of the methods used in cryotherapy. It is well known that exposure to extremely low temperatures in the human body induces metabolic, hormonal, and thermoregulatory reactions. The study aimed to investigate whether repeated whole-body cryotherapy treatments would have an impact on the colonization of *Staphylococcus aureus* in individuals with atopic dermatitis (AD).

Methods: Fourteen adults with a mean age of 32 ± 10.8 and mild to moderate AD (mean of SCORAD index 36.5 points) were enrolled in the study. Whole-body cryotherapy comprised a total of 15 treatments, once a day.

Results: In the following research, it has been observed that whole-body cryotherapy treatments have an impact on the colonization of *Staphylococcus aureus* on the skin of patients with AD. It would be beneficial to include a larger sample size of AD patients, including both those receiving W-BC treatments and those who do not.

Conclusions: Based on the following research, W-BC can be considered an effective adjunctive method in the treatment of AD.

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Keywords: body cooling, cryotherapy, swabs, *Staphylococcus aureus*, atopic dermatitis

INTRODUCTION

The cause of eczema is multifactorial, involving both genetic and environmental factors. These factors affect both the epidermal and immune phenotypes, with T helper 17 (Th17) cells playing a contributing role. *In vitro* studies have demonstrated the impact of immune cell mediators, such as histamine, on keratinocyte differentiation, highlighting the close relationship between the epidermis and the immune system. Environmental exposure and individual susceptibility may impact multiple pathways, leading to varying degrees of dysfunction in the skin barrier and immune system regulation [1]. As a result, the common symptom of atopic dermatitis (AD) is pruritus, which can reduce patients' quality of life. Additionally, itching of the skin is exacerbated by emotional stress or sleep [2].

Research has indicated that individuals with atopic dermatitis possess a less diverse skin microbiome, which is identified by an elevated abundance of *Staphylococcus aureus* (*S. aureus*). This, in turn, has been associated with the severity of the disease in patients with AD [3]. *Staphylococcus aureus* not only causes skin infection but also produces virulence factors such as biofilm, superantigens, α-toxin, and protein A. The biofilm's role is to protect pathogenic bacteria from host immune cells [4].

Whole-body cryotherapy (W-BC) is one of the methods used in cryotherapy. The procedure is based on the effect of a thermal stimulus at an extremely low temperature ranging from –100°C to –160°C for a short period, typically 2–3 minutes on the human body [5, 6]. Whole-body cryotherapy has been used as a physiotherapy method for a long time,

Address for correspondence:
Magdalena Kępińska-Szyszkowska, University of Physical Education in Krakow, Jana Pawła II 78, 31–571 Kraków, Poland, e-mail: magdalena.kepinska@awf.krakow.pl

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utilizing cryogenic temperatures (below –100°C) to induce and exploit physiological reactions in the human body to extreme cold. This action occurs in two stages. The first phase is characterized by stimulation of the sympathetic nervous system, resulting in vasoconstriction of the blood vessels in the skin and subcutaneous tissue. Blood pressure and metabolic activity increase as a result of the body's defensive reaction to the cold, although temperature decreases. Vasoconstriction leads to tissue cooling and poorer oxygen and nutrient supply, slowing down metabolic processes. This stage is relatively short. Then, there is vasodilation and tissue hyperaemia [5–7].

Increased blood flow and oxygenation of the muscle tissue can reduce lactate and histamine levels, increase bradykinin and angiotensin levels, and stimulate the release of endogenous beta-endorphins [7, 8]. The intended effect of this cold exposure is to reduce pain, inflammation, and post-traumatic swelling [5, 6]. Cryotherapy has also shown a marked effect on the psychological condition of the patient, leading to a more positive attitude and mood. Many individuals experience a sense of relaxation, calmness, and overall relief. Physical relaxation is also reported as a beneficial effect. Discomfort associated with pain and fatigue decreases, despite their intensification before the treatment. The state of well-being persists for several hours after the procedure, or even longer. The physiological benefits of exposure to extremely low temperatures have practical applications in biological rejuvenation, various sports disciplines, and the treatment of anxiety and depression [5–7].

The study aimed to investigate whether repeated whole-body cryotherapy treatments would have an impact on the colonization of *S. aureus* in individuals with AD.

MATERIAL AND METHODS

Patient characteristics

This study does not include randomization (single-arm clinical trial). The participants were recruited *via* a posted advertisement at the health clinic in Krakow. Inclusion criteria included age over 18 years, no contraindications to W-BC treatment and clinical diagnosis of atopic disease (mild to moderate). Study exclusion criteria included: lack of informed consent for the study; patients being treated for AD with phototherapy, cyclosporine A, oral corticosteroids, topical calcineurin inhibitors such as pimecrolimus and tacrolimus; patients during or after immunotherapy; children and adolescents under 18 years of age; lactating mothers; pregnant women; and patients with inflammatory, infectious, autoimmune, or cancerous diseases. An analysis of AD was conducted based on a questionnaire completed by patients in the presence of a dermatologist [8]. The questionnaire included basic information such as disease duration, symptoms, treatment, allergy diagnostics, and family history. The next stage involved assessing the level of AD advancement based on the SCORing Atopic Dermatitis (SCORAD) [9]. The major and minor AD criteria presented by Hanifin and Rajka [10] were also taken into consideration. Fourteen adults with a mean age of 32 ± 10.8 (7 men and 7 women) and mild to moderate AD (mean of SCORAD index 36.5 points) were enrolled in the study. The subjects were adults who lived in a big city and had been suffering from AD for a long time. Most of them experienced disease exacerbations every few months, and the severity of AD showed annual seasonality [8].

The study was conducted by the Declaration of Helsinki. All subjects gave their informed consent for inclusion before they participated in the study. The methodology of the scientific project was approved by the Bioethics Committee at the District Medical Chamber in Krakow, Poland, with opinion No. 239/KBL/OIL/2018. The study was registered at ClinicalTrials.gov under the number NCT03761199.

Sample collection

All samples were obtained from AD patients at the Centre for Microbiological Research and Autovaccines in Krakow, Poland. Nasal swab specimens were collected using a sterile cotton-tipped swab by approaching upward toward the top of both nares, followed by a 360° twist to cover the entire vestibule. In addition, skin swabs were taken from the AD patients by rolling a sterile cotton-tipped swab stick over their worst affected skin areas twice for at least 5 seconds [11] (right elbow flexion, left elbow flexions, neck, the area between the shoulder blades, lumbar region, right knee flexion, left knee flexion).

Laboratory analysis of *S. aureus* isolates

Bacterial cultures of the nasal and skin swabs were performed using standard laboratory techniques. The identity of *S. aureus* was confirmed based on colony morphologic features, coagulation of citrated rabbit plasma with EDTA, and production of clumping factor and protein A [11]. Bacterial growth was classified as follows: (0) no bacteria, (1) single < 10 CFU/mL, (2) few 11–50 CFU/mL, (3) plentiful 50–200 CFU/mL, (4) connected uncounted > 200 CFU/mL.

Whole-body cryotherapy procedures

Whole-body cryotherapy comprised a total of 15 treatments, once a day, at the Malopolska Centre for Cryotherapy, al. Pokoju 82, in Krakow, Poland. After consulting with a physician to exclude contraindications for W-BC, patients were referred for treatments. Patients entered the cryogenic chamber wearing special shoes, thick socks, shorts, gloves,

Table 1. The skin swaps measured before the first treatment (I), after the 15th treatment (II) and after 3 weeks from the end of W-BC therapy (III)

Part of the body	I	II	III	p-value
		M (Q25–Q75)		
1. Nasal swap right side	1 (0–2.75)	1.5 (0–3)	1.5 (0–3)	II *vs.* I III *vs.* I
2. Nasal swap left side	1.5 (0.25–2)	2 (0.25–3)	2 (0.25–3)	II *vs.* I
3. Right elbow flexion	1 (0–3)	1 (0–1.75)	1 (0–1.75)	NS
4. Left elbow flexions	0 (0–2.5)	0.5 (0–1)	0.5 (0–1)	II *vs.* I III *vs.* I
5. Neck	0 (0–1)	0 (0–1)	0 (0–1)	NS
6. The area between the shoulder blades	0.5 (0–1)	0 (0–1)	0 (0–1)	NS
7. Lumbar region	0 (0–1)	0.5 (0–1)	0.5 (0–1)	II *vs.* I III *vs.* I
8. Right knee flexion	1 (0–1.75)	1 (0–1)	1 (0–1)	II *vs.* I III *vs.* I
9. Left knee flexion	0.5 (0–1)	0.5 (0–1)	1 (0–1)	II *vs.* I III *vs.* I

(I–III) — measurement number; *vs.* — *versus*; NS — non-statistical; $p < 0.0001$; M — median and (Q25–Q75) the value of the lower and the upper quartile of classification of bacteria; (0) — no bacteria, (1) — single < 10 CFU/mL; (2) — few 11–50 CFU/mL, (3) — plentiful 50–200 CFU/mL, (4) — connected uncounted > 200 CFU/mL

and headwear. To acclimate the body to low temperatures, patients spent 1.5 minutes in the main chamber on the first day, 2 minutes on the next day, and then 3 minutes for the remainder of the therapy. The W-BC sessions took place during the winter of 2018/2019. Patients refrained from using local anti-inflammatory preparations and systemic antihistamine drugs for one week before the therapy and throughout the study. Participants began the cooling process in the vestibule, where the temperature was –60°C, for 30 seconds. They then proceeded to the main chamber, where the temperature was –120°C. Patients were continuously monitored by an operator inside the chamber using thermal glass and intra-chamber monitoring. A phonetic communication system allowed the operator to inform patients about the remaining treatment time. In case of feeling unwell, patients had access to an alarm button and an exit device designed to open the door from the inside [8].

Statistical analysis

Non-parametric statistics (Wilcoxon signed-rank test) were used to compare post-treatment data with the baseline due to the small number of participants and the lack of normal data distribution. Throughout the subsequent sections and tables, the median (M) and the values of the lower and upper quartiles (Q25–Q75) are reported. A p-value of less than 0.05 was considered statistically significant. All statistical analyses were performed using Statistica 13 software (StatSoft, Inc., USA).

RESULTS

Eight out of fourteen patients completed the treatment period (5 women and 3 men). Two patients discontinued the study due to worsening dermatitis, while the other four patients left for reasons unrelated to their skin condition. In one subject with AD, no *S. aureus* was detected in the tested swab areas. In the remaining individuals, MSSA bacteria were present, and the result depended on the swab site and the number of W-BC procedures [8].

Significant differences were observed in the nasal swab samples, showing an increasing trend in the number of *S. aureus* compared to the pre-W-BC result ($p < 0.0001$). On the other hand, in exposed body parts such as the neck and the area between the shoulder blades, no statistically significant changes were observed, but a decreasing trend was noticed. However, in covered body parts such as the lumbar region, left and right knee flexion, and the exposed left elbow flexion during cryotherapy, an increase in the number of *S. aureus* was observed when comparing the second and third measurements to the pre-W-BC state ($p < 0.0001$), as shown in Table 1.

DISCUSSION

The presented study aimed to examine the impact of a series of W-BC treatments on *S. aureus* colonization in individuals with AD. There is very limited data in the available literature regarding the use of whole-body cryotherapy in dermatological issues, including AD therapy. To the best of the authors' knowledge, this study is the first to demonstrate the influence of low temperatures on *S. aureus* colonization in patients with AD.

It is estimated that *S. aureus* is present in over 90% of AD skin lesions. In contrast, only 5% of healthy individuals are carriers of this organism, with the main site of colonization being the nose [11]. In the following study, only one subject

with AD did not show any detectable *S. aureus* in the tested swab areas, while the remaining individuals had MSSA bacteria detected, consistently confirmed in each swab sample. The subjects were carriers of *S. aureus*, as indicated by the presence of the bacteria consistently.

It is widely known that exposure to extremely low temperatures in the human body induces metabolic, hormonal, and thermoregulatory reactions. Low temperatures also stimulate the sympathetic nervous system and cause vasoconstriction, which persists for about a minute after the procedure. Following the treatment, the dilation of internal organ blood vessels reduces the levels of lactate and histamine, alleviates pain and has a positive influence on morphological, rheological and biochemical blood parameters [5–8, 12]. The lowering of body temperature also leads to a decrease in nerve impulse transmission. Another significant effect of prolonged cold exposure is the increased secretion of thyroid and adrenal hormones, as well as an elevated cellular metabolism. The impact on sensory receptors results in reduced pain sensations, as nerve impulses do not reach the neural cortex. Additionally, cold exposure activates the "endogenous opioid system", responsible for the production of β-endorphins, which are endogenous substances similar to morphine [5–8]. These findings explain the observed beneficial changes in skin parameters in previous studies. The series of W-BC treatments reduced skin irritations, including itching and inflammation (a mean SCORAD index decreased after cryotherapy treatments) in patients with AD. Furthermore, in healthy and AD individuals, cryotherapy did not lead to any adverse effects and was well tolerated [8, 9].

During W-BC treatments, the skin temperature rapidly decreases. The lowest temperatures are observed on the forearms and lower limbs (calf), while the highest temperatures are found on the palms and the soles of the feet, as they are protected by gloves and socks [13]. As reported by Cholewka et al. [14], the decrease in skin temperature also depends on the magnitude of the low temperature that affects the body and the duration of time spent in the cryogenic chamber. In the present study, a decreasing trend in the number of *S. aureus* was observed in exposed areas, while a slight increase was noticed in the covered body parts. Comparing the measurements between the third and second sessions (in each of the tested body areas), it was observed that the number of *S. aureus* remained at the same level. This suggests that cryogenic temperatures may influence the activity of bacteria on the skin by inhibiting the proliferation of *S. aureus*, especially in areas of the body exposed to low temperatures.

CONCLUSIONS

Due to the limited sample size, the results of this study are considered hypothetical. Based on the present research, W-BC can be considered an effective adjunctive method in treating AD. W-BC treatments have an impact on the colonization of *S. aureus* on the skin of individuals with AD. Depending on the body area, a decreasing trend in the number of *S. aureus* (in exposed body areas) and an increasing trend (in covered body areas) were observed. However, there is still limited data available in the scientific literature regarding the impact of cryogenic temperatures on skin parameters in patients with AD. The present study has several limitations. It would be beneficial to include a larger sample size of AD patients, including both those receiving W-BC treatments and those who do not.

Article information and declarations

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Data availability statement

The data used to support the findings of this study are included in the article.

Ethics statement

The study was conducted by the Declaration of Helsinki. The methodology of the scientific project was approved by the Bioethics Committee at the District Medical Chamber in Krakow, Poland, with opinion No. 239/KBL/OIL/2018. The study was registered at ClinicalTrials.gov under the number NCT03761199. All subjects gave their informed consent for inclusion before they participated in the study.

Author contributions

Study concept and design — MK-Sz, AM, MK-M, KR; methodology and investigation — MK-Sz, AM, MK-M, KR; data collection — MK-Sz, AM, KR, MK-M; data analysis — MK-Sz, AM; writing-original draft preparation — MK-Sz; writing-review and editing — MK-Sz, AM. All authors have read and agreed to the published version of the manuscript.

Conflicts of interest

The authors declare no conflict of interest.

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Supplementary material

None.

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