OSTEPATHIC MANIPULATIVE TREATMENT AND WHOLE-BODY CRYOTHERAPY FOR ATOPIC DERMATITIS A RANDOMISED CONTROLLED CLINICAL TRIAL

Master´s thesis for obtaining the academic degree

Master of Science

in the study programme Osteopathy MSc

submitted by

Monika Lammeraner

Department for Health Sciences, Medicine and Research

at University for Continuing Education Krems

Advisor: Isabelle Schüssler Msc

Advisor: Dr. Andreas Brandl MSc D.O.

Krems an der Donau, May 30, 2025

STATUTORY DECLARATION

I, Monika Lammeraner, hereby declare:

I have written my Master's thesis myself and have not used other sources than the ones stated and moreover have not used any illegal tools or other unauthorised aids.

The following AI-supported tools were used to support my scientific research:

- quillbot.com for verifying the text accuracy, spelling and grammar
- chatGPT for text revison

I am solely responsible for all content of my work, including passages generated or supported by AI-supported tools, and I am solely responsible for complying with scientific standards.

I have not used my Master's thesis or parts thereof as an exam paper domestically or in a foreign country in any form to this date.

In case my Master's thesis concerns my employer or any other external cooperation partner, I have fully informed them about title, form and content of the Master's thesis and have his/her permission to include the data and information in my written work.

Date: May 30, 2025

Signature: 

Atopy (Greek *ατοπία*): the state of being out of place, absurdity

DEAR

M H F P

O U R A

T S I T

H B E I

E A N E

R N D N

D S T

S

Special thanks go to my mum, who sent me to English lessons, thanks to which I experienced many adventures and met my supportive husband, to whom I dedicate this work. I also want to thank my friends and patients who put faith in me and helped spread the word, making this project possible. Thank you, dear, for these extra 96 words, sense of humour, and some freedom.

ABSTRACT ENGLISH

Background:

Atopic dermatitis (AD) affects every tenth adult and even more youngsters in developed countries. As more people are using alternative therapies, there is a growing need for clear and unbiased information. The aim of the study was to compare the effectiveness of whole-body cryotherapy (WBC) and osteopathic manipulative treatment (OMT) in patients with AD.

Methods:

10 adults with mild-to-severe AD participated in this open randomised controlled clinical trial. Participants were randomly allocated to either: the control group (10 WBC sessions) or the experimental group (3 OMT treatments). The participants measured their AD severity score with the self-administered Eczema Area and Severity Index (SA-EASI) at baseline, after a 3-week treatment period, and at the 6-week follow-up.

Results:

There was a significant difference between the groups on the acute AD severity ($p < .001$) and on the total AD severity ($p = 0.002$). Differences regarding chronic AD scores and the lesional surface were not statistically significant.

Conclusions:

Both WBC and OMT improved the disease severity, but in a different way. WBC resulted in a sharp reduction in acute AD severity (from 5.85 to 1.9), but this effect diminished over six weeks, with severity nearly returning to baseline (5.03). In contrast, OMT showed a more sustained improvement (mean scores of 5.73, 2.77, and 3.87), indicating a potential advantage for long-term management and maintenance therapy.

Keywords:

atopic dermatitis, whole-body cryotherapy, osteopathic manipulative treatment

ABSTRACT GERMAN

Wissenschaftlicher Hintergrund:

Atopische Dermatitis (AD) betrifft jeden zehnten Erwachsenen und noch mehr Jugendliche in entwickelten Ländern. Da immer mehr Menschen alternative Therapien nutzen, besteht ein wachsender Bedarf an klaren und unvoreingenommenen Informationen. Ziel der Studie war die Untersuchung der Wirksamkeit der Ganzkörperkältetherapie (WBC) und der osteopathischen Behandlung (OMT) bei Patienten mit Neurodermitis (AD).

Methodik:

An dieser offenen, randomisierten klinischen Studie nahmen 10 Erwachsene mit leichter bis mittlerer Neurodermitis teil. Es gab 2 Behandlungsgruppen: die Kontrollgruppe (10 WBC-Sitzungen) und die Versuchsgruppe (3 OMT-Behandlungen). Die Teilnehmer maßen ihren Schweregrad der atopischen Dermatitis mit dem Ekzem-Flächen- und Schweregrad-Index (SA-EASI) zu Beginn, nach einer 3-wöchigen Behandlungsperiode und beim Follow-up nach 6 Wochen.

Ergebnisse:

Es gab einen signifikanten Effekt der Gruppe auf das akute Ergebnismaß ($p < .001$) und auf das totale Ergebnismaß des Schweregrades der atopischen Dermatitis ($p = 0.002$), was bedeutet, dass sich die Interventionsgruppen erheblich unterschieden. Die Unterschiede zwischen dem chronischen Ergebnismaß und der Läsionsoberfläche waren statistisch nicht signifikant.

Conclusio:

Sowohl eine Ganzkörperkältetherapie als auch eine osteopathische Behandlung verbesserten die Symptome, aber auf unterschiedliche Weise. Eine Ganzkörperkältetherapie führte zu einem signifikanten Rückgang des akuten Ergebnismaßes (von 5.85 auf 1.9), aber nach 6 Wochen war es wieder auf nahezu Ausgangsniveau (5.03). Eine osteopathische Behandlung scheint einen leichten Vorteil gegenüber der Ganzkörperkältetherapie zu haben, da die Mittelwerte nachhaltiger abnahmen (5.73, 2.77 und 3.87), was darauf hindeutet, dass es besser für die Langzeittherapie geeignet sein könnte.

Schlüsselwörter (Autor innenschlagwörter):

atopische Neurodermitis, Ganzkörperkältetherapie, Osteopathie

TABLE OF CONTENTS

1 Introduction

Since the 2010s, understanding of atopic dermatitis (AD) has improved significantly, leading to proactive strategies and effective systemic therapies. As a result, complementary approaches have gained attention - likely due to the condition's relapsing nature and concerns over drug side effects (Lal et al., 2016).

Dermatology is one of the youngest osteopathic medical specialties; the first organisation uniting specialists in this discipline, the American College of Dermatology (AOCD), was founded over twenty years after other specialisations. Despite the rare application of osteopathic manipulative treatment (OMT) for skin diseases, its potential benefits remain undiminished. Fast-paced dermatology conditions may not support its routine usage; nevertheless, OMT could be applied - alone or as a complementary therapy - to improve outcomes for patients with demanding cutaneous disorders. Knowing OMT's potential benefits, even specialists who are unfamiliar with them may send patients to OMT (Campbell et al., 2011).

AD affects up to 20% of children and 10% of adults in developed countries. The onset in infancy or early childhood is most common, but it can happen at any age. Various symptoms are present, but intense itching and repetitive eczematous lesions remain hallmark features. Researchers have linked sleep deprivation, low self-esteem, and psychological stress to the severity of AD. It also has a complex origin; a genetic factor with a change that stops the gene that codes for filaggrin (a skin structural protein) is a major contributing component. Upregulation of genes encoding for Th2 cytokines, like IL-4, IL-13, and IL-33, as well as polymorphisms in a gene encoding for those cytokines' receptors, are also involved. A genetically determined skin barrier deficiency, which shows up as dry skin, may often be the first step in the aetiology of AD. Aside from the skin barrier, environmental reasons are relevant, as people with AD tend to suffer from allergic rhinitis, asthma, and food allergies as well. Both physiological and psychological stressors trigger the disease. Over the past 30 years, AD incidence has increased dramatically (Langan et al., 2020; Stefanovic et al., 2020).

AD diagnosis typically involves a combination of a clinical evaluation, patient history, and sometimes skin biopsies. Currently, diagnostic guidelines are only relevant for scientific enquiries and not for clinical use. According to a 2020 decision by the European Task Force for Atopic Eczema, dermatologists' clinical judgement has a diagnostic capacity much above

any currently existing diagnostic criteria. Serum-specific indicators for the diagnosis of AD are not yet available.

European recommendations from 2018 provide a four-step process for treating AD depending on the EASI (Eczema Area and Severity Index) score. It is based on the evaluation of four clinical parameters: skin redness, oedema, signs of scratching, and thickening of the skin (Hanifin et al., 2022; Lobefaro et al., 2022). There are multiple tools for assessing the severity of the illness; the mentioned scale has the highest interrater reliability, whereas the equally prevalent SCORAD (Scoring Atopic Dermatitis), ought to be chosen when various physicians conduct assessments (Bożek & Reich, 2017).

Appropriate treatment varies depending on the severity of the disease. In benign cases, topical medications are sufficient, while systemic medications are required in moderate to severe cases. 2017 Dupilumab significantly changed the treatment of severe AD by blocking the action of both IL-4 and IL-13, two key cytokines involved in the pathogenesis of AD (Langan et al., 2020; Lobefaro et al., 2022). Identification and avoidance of any trigger factors form the cornerstone of AD treatment. Conventional immunosuppressive medications and systemic corticosteroids have short- and long-term side effects that make them unsuitable for long-term usage, particularly in moderate-to-severe AD. There are still several clinical requirements not met in patients with AD, despite recent advances in understanding the pathophysiology and treatment of the disease (Lobefaro et al., 2022).

With noninvasive OMT techniques that target the physiology underlying particular conditions, it may be possible to avoid adverse side effects. The branch of medicine dealing with the skin, as an all-round specialty, is at one with the osteopathic principles (1. the person as a unit; 2. the capability of self-regulation and self-healing; 3. structure-function interrelation; 4. understanding these concepts is the foundation of rational treatment) and exemplifies Still's point of view (Campbell et al., 2011; Giesey et al., 2020).

The osteopathic structural exam may help find areas of possible inflammation by looking for changes in tissue texture, tenderness, and limited motion. These findings are referred to as somatic dysfunction. An imbalance in the autonomic nervous system is linked to the development of AD, since low vagal tone is linked to inflammatory disorders (Lal et al., 2016).

AD, as a source of somatic dysfunction, affects not only the palpable skin but also the immune and lymphatic systems, surrounding fascia, and patients' mental wellness as well. Myofascial release, soft tissue technique, and lymphatic pump technique seem here to be

useful modalities and have been described in various papers (Giesey et al., 2020; Hibler et al., 2014; Leone et al., 2018).

After finding the area of myofascial strain in patients with AD, restricted areas can be palpated and myofascial release applied. It is hypothesised that psychological stress was less due to cervical relaxation performed in that trial (Hosono et al., 2020). This is not to be underestimated, as approximately 1 in 6 individuals with AD had clinical depression, 1 in 4 felt depressed, and 1 in 8 experienced suicidal thoughts (Patel et al., 2019).

The lymphatic pump technique may be applied to the thoracic cage (thoracic pump), abdomen (abdominal pump), legs (pedal pump), and the aspects of the liver and spleen. It improves lymphatic circulation, reduces oedema and helps fight infections (Hodge & Downey, 2011). Depending on the spot of the AD flare, the clinician can address one of four physiological membranes: tentorium cerebelli, superior thoracic aperture, and both abdominal and pelvic diaphragms. Even patients themselves could perform the fairly simple lymphatic techniques. This also applies to myofascial release and multiple soft tissue techniques. These techniques may loosen up the enclosing fascia, improve the lymphatic flow, stretch tissues, improve oxygenation and nutrition, and improve immune system responses in the area (Leone et al., 2018).

The search terms "osteopathic manipulative treatment and atopic dermatitis" currently return only two results on PubMed. The lack of standardised studies necessitates more controlled trials to confirm the effectiveness of OMT for dermatological diseases.

Every second individual suffering from this common inflammatory disorder decides to use complementary or alternative medicine (Simpson et al., 2003). Therefore, there is a huge need in this field for objective information.

1.1 Epidemiology

Since the 1960s, the prevalence of AD has significantly increased in the general population. By the end of the 20th century, the tripling of AD in the previous three decades had affected about 10% of the world. Between 1939 and 1964, the prevalence rates in different populations were only 1-3%. Investigations conducted from 1980 to 2005 revealed significantly higher figures, ranging from 26% for questionnaire-based studies to 32% for real investigations with dermatological tests. Estimates generally suggest that 3% of adults and 12% of preschoolers are impacted, with figures in the general population regularly fluctuating between 1% and 25%. The prevalence of AD declines with age, with estimates

ranging from 10% to 13% for children and 2% to 10% for adults (Drucker et al., 2017; McKenzie & Silverberg, 2019; Saloga et al., 2006).

1.1.2 Contributing factors

The reasons behind the increasing prevalence of this condition remain unclear. One of the most popular hypothetical explanations is the „hygiene hypothesis." This phrase describes inadequate immune system stimulation and suggests early exposure to microbes can reduce allergy risk. In reverse, the preventive effect of traditional farm life is noteworthy, which is known as „the farm effect". Besides, owning a dog seems to have a similar impact. Socioeconomic status and atopic sensitisation typically have a positive correlation. Uncertainty surrounds the correlation's cause – perhaps excessive hygienic practices. However, concluding that it is a sickness that just affects the rich would be incorrect (Hesselmar et al., 2015). Experiences report a high prevalence in Oceania, Sub-Saharan Africa, and the slums in US inner cities. The frequency is higher among Blacks and Hispanics: their families' income, Medicaid, care availability, and the challenge of diagnosing erythema in non-white skin may result in a delayed or inadequate diagnosis. In general, compared to Asia and Eastern Europe, Australia and Northern Europe appear to have greater rates of AD prevalence (Ring, 2016).

Growing urbanisation trends could be a factor in the overall rise in AD frequency. Environmental variables like hygiene changes, antibiotic use, and pollution may increase prevalence in urban areas. Traffic exhaust is the most important trigger outdoors, and environmental tobacco smoke indoors, particularly with atopic parent(s) (Bonamonte et al., 2019). One study found that infants whose parents sucked pacifiers to clean them were less likely to develop eczema and asthma (Hesselmar et al., 2013). Another study revealed that children in houses with hand-washed dishes had fewer allergic reactions compared to those using a machine, possibly due to increased microbial exposure (Hesselmar et al., 2015). Further, adequate skin care is crucial; newborns can benefit from emollients for prophylaxis, but too intensive procedures may eliminate cutaneous microbiota. There are differing views on breastfeeding, even though maternal nutrition seems to have no impact, while extended gestation carries a higher risk. Errors in nutrition can start AD and cause flare-ups. Nuts have been the subject of extensive research. The German word for AD, „neurodermitis," suggests clearly that psychological factors may contribute to the onset and worsening of

symptoms. Psychological aspects can significantly influence disease pathways, both positively and negatively (Ring, 2016).

Although the pathophysiology of AD is generally believed to be allergic and inflammatory, there is growing evidence that suggests the disease could also have an autoimmune component (Ring, 2016). Genetics strongly influences atopic disorders; monozygotic twins exhibit about 80% concordance. If one parent has atopic disease, the child's risk increases to over 30%, and if both parents are affected, the risk increases to 60% (Saloga et al., 2006). In contrast to straightforward Mendelian heredity, AD is a complicated disease that exhibits polygenic inheritance under multivariable influence and partial genomic imprinting (maternal influences being greater than paternal ones). Molecular genetics has identified chromosomal regions associated with AD's markers. Genes like filaggrin (and maybe hornerin) that are part of the epidermal differentiation complex are especially important for raising the risk of eczema (Ring, 2016). Though only 40% of individuals with filaggrin mutation get AD, it is the biggest hereditary risk. People who carry the filaggrin mutation have a unique phenotype that is linked to atopic comorbidities (Stefanovic et al., 2020).

1.1.3 Symptoms over a lifetime

The disease is largely hereditary, but it doesn't necessarily have to manifest right after birth or in infancy. It can first appear at any age, heal, or not show up for years or even decades. When one gets older, there is a trend toward regression; nonetheless, fresh exacerbations or true initial diseases can still happen. Different manifestations occur at different stages of life. Itch is a dominant symptom that affects people at every stage of life and may lead to sleep disorders (Saloga et al., 2006).

It is possible to distinguish between three different clinic forms; about one-third of the patients exhibit each of them:

- eczema disappears in early childhood
- eczema disappears by puberty but will come back
- eczema persists from childhood into adulthood (Kissling & Wüthrich, 1993)

Infants: a common misconception is that eczema exists already at birth. About 50% of cases usually start showing symptoms around the third month of life, occasionally, even within the first month of life. Differential diagnosis in newborns is difficult; the term „infantile eczema" is in regular use. Crusta lactea with dandruff on the scalp is the first classic onset.

Furthermore, erythema, blisters, and papules on cheeks can appear. As a result of scratching, crusts might form. Superinfections caused by bacteria are not uncommon, frequently resulting in local lymph node enlargement. In half of the cases, eczema heals entirely within a few months. The other half still has exacerbations that alternate with periods of clear skin. Among the variables linked to a poor prognosis are the onset before the sixth month of life, extreme manifestation of eczema, being a single child, elevated IgE in serum, and concomitant respiratory atopy symptoms (Ring, 2016; Saloga et al., 2006).

Children: the predilection sites are mainly the joint folds (elbow creases, wrists, and knee pits - „eczema flexorum") as well as the hands and feet, and additionally the face: particularly the cheeks and neck. There is generally dry skin in the affected areas. The skin is red, oozes, especially after scratching, is crusty, or rather chronically eczematous, thus altered by lichenification. Furthermore, there are locally limited eczema patches corresponding to local trigger factors (for example, eczema on the thumb as a result of thumb-sucking or perioral eczema following repeated lip-licking). The increase in lymph nodes due to dermal inflammation intensifies with superinfections. About half of the cases also develop bronchial asthma and/or allergic rhinitis. In early childhood, boys appear to be more affected, yet other investigations show higher rates in girls compared to boys. Though the majority of cases of AD likely begin before the second year of life, the number of patients exhibiting or developing it in adulthood is on the rise (Ring, 2016; Saloga et al., 2006).

Adults: there are the same predilection sites as in childhood, with hand eczema being particularly prevalent in cases of occupationally-induced skin exposure. With chronic persistence, changes such as lichenification become more pronounced, and the tendency toward nodular lesions (prurigo nodularis) increases. Secondary inflammation-related damage is also more common: hair loss, nail dystrophies, or loss of the lateral eyebrows. Hair is often dry and dull, nails are often shiny due to frequent scratching, and there is sometimes pronounced conjunctivitis (probably from constant rubbing). When persistent eczema appears newly in adulthood, females are typically more affected than males. Generally, the ratio of affected women to men is 2:1. The literature has often ignored the newly emerging AD in the elderly, misdiagnosing it as „generalised eczema of unknown origin" (Ring, 2016; Saloga et al., 2006).

1.2 Pathophysiology

Beyond being the biggest organ in the body, the skin serves as a barrier against toxins, water loss, and electrolyte imbalance, as well as an external layer of defence (SALT – skin-associated lymphoid tissue). The skin is a sensory organ that allows direct contact with our environment, sometimes painfully. It also mirrors our inner mood and emotional state (Schneider, 2013).

The epidermis is the outermost layer of the skin and is composed of four layers: basal, spinal, granular, and corneal. Elastin and collagen fibres, specialised nerve endings, and plenty of blood vessels make up the dermis, which is a connective tissue layer. The lowest hypodermis is a subcutaneous tissue that connects the skin to the underlying tissues: muscle or bone (Sherwood, 2010).

An animation of the histology picture in the epidermis would reveal two dynamically moving levels that self-replace every two and a half months. The cube-formed cells are pushed to the surface (and away from their nutrient supply) until they die and flatten as a result of „wear and tear." As the outer cells constantly peel off and are replaced, the protective keratinised layer remains. Keratinocytes are the most common epithelial cells and produce keratin, which is the most important type of protein in the human body. They are also immune system cells that produce important cytokines like IL-1 and IL-6. Langerhans cells, the most exterior immune system's guardians, originate from the bone marrow and, as macrophages, dwell in the epidermis, where they present antigens. Therfore, when invading microorganisms breach the skin barrier, the skin signals lymphocytes for action. Small molecules under 800 kilodaltons with lipo- and hydrophilic characteristics primarily compromise the skin's barrier function, enabling the application of topical medications. The skin's acidic surface film shields it against environmental aggressors, including germs and drying out (Sherwood, 2010 & Schneider, 2013).

1.2.1 First itch

Dermatologists typically begin with the primary lesion when describing skin diseases, but AD does not entirely provide their assent. Jaquet (1904) emphasised the symptom „pruritus". He supposedly remarked, along with Johann Wolfgang von Goethe (Faust) and Saint John the Evangelist, that „in the beginning there was the itch." Unlike pain, society and many physicians often take itching lightly. Considered to be „incurable", it is the most excruciating sign of a manifest illness. The symptoms, which include sleeplessness, nighttime scratch

attacks with bloody bedding, and a helpless feeling are inescapable symptoms. Together, discomfort and itching produce significant AD symptoms. Itching, as „dermatose invisible," causes characteristic morphologic skin alterations through scratch reaction. Seldom can the acute growth of eczematous lesions be seen in AD directly, but cutaneous damages might appear due to psychological or environmental triggers in people who have never displayed any indications of these changes. After several hours, a typical clinical manifestation appears (Ring, 2016).

Proinflammatory substances are released when the skin is scratched, marking a pathophysiological turning point. Recently, researchers discovered a connection between itching in atopic skin inflammation and activated T cells. AD increases IL-31, a cytokine that significantly contributes to pruritus. The AD pruritic sensation is associated, at least partially, with Staphylococcus aureus, which causes even greater discomfort (Kasraie et al., 2010).

1.2.2 Complex disease mechanism

S. aureus species colonise 30% to 100% of atopic skin, increasing itch severity and causing itch-inducing cytokine IL-31 in the skin and peripheral blood. As a result of S. aureus development, cutaneous commensal bacteria are driven out, resulting in dysbiosis – a disorder in which the symbiotic relationship is disrupted and the resident commensal community is altered (Petersen & Round, 2014). These inadequacies often result in clinical observation of skin infections of diverse aetiologies in AD patients (Nakatsuji & Gallo, 2019).

A genetically predetermined skin barrier defect that appears as dry skin is frequently the first step in the aetiology of AD. Although filaggrin genetic mutation is less common in non-white AD patients, its identification in 50% of white AD individuals offered new insights into disease mechanisms (Park et al., 2016). It is not known yet if there is perhaps another skin barrier protein effect. Fillagrin is a crucial protein in the development of a normal skin barrier, formed from profilaggrin within keratohyalin granules. It plays a role in aggregating keratin filaments and maintaining successful molecular epithelium. Individuals with AD have less hydrated skin, causing extra transepidermal water loss and xerosis. Loss of skin barrier enhances irritant and allergen penetration (Rodríguez et al., 2009).

When the epidermal barrier is damaged, pro-inflammatory cytokines are made in large amounts. This activates innate lymphoid cells and T helper cells (TH2/TH22). Histologically, intercellular oedema of the epidermis and mononuclear cell invasion are hallmarks of acute AD. Eosinophils and mast cells are drawn in, and IL-31 is released. These actions are mostly

caused by IL-4 and IL-13 (Stefanovic et al., 2020). Distinct epidermal features, such as hyper- or dyskeratosis (abnormal keratinisation), intercellular oedema, and a moderate amount of lymphocytes, mast cells, and monocytes/macrophages, are present in chronically inflammatory lesions. AD is characterised by increased serum levels of cytokines like IL-1 and IL-6, which could lead to a higher risk of cardiovascular and cerebrovascular comorbidities. The superantigen from S. aureus increases the production of IL-31 and, indirectly IL-1 (Zhang et al., 2017).

Research indicates a connection between atopic symptoms and immunological deviations of the skin, gut, and lungs. Initial skin disruption allows allergen sensitisation and colonisation by pathogens, leading to a Th2 inflammatory response and thymic stromal lymphopoietin-mediated pathway. Thymic stromal lymphopoietin (TSLP) initiates immune responses in epithelial cells following injuries, cytokine stimulation, or infection, indirectly by binding allergens. This may explain the atopic march phenomenon, which commonly manifests as skin atopy but later affects other organ systems. AD, allergic rhinitis, and asthma are collectively known as the atopic march. Atopic patients also frequently experience other allergy disorders such as food allergies, allergic conjunctivitis, and eosinophilic oesophagitis (Han et al., 2018). To sum up, AD is caused by three main factors: damage to the skin barrier, immune response disorders, and and imbalance in the skin microbiome. These are all brought about by genetic changes and environmental factors.

1.2.3 Daily burden

AD symptoms disrupt normal lifestyles, causing patients to avoid social interactions and impacting daily activities like sports. Children often feel embarrassed and socially isolated, which lowers their quality of life. Over 60% of kids struggle with sleep, leading to mood swings, fatigue, and even growth hormone disorders. When compared to other serious conditions, including cancer, diabetes, and myocardial infarction, the quality of life is reduced to an equivalent or greater degree (Lewis-Jones, 2006).

AD has the most disability-adjusted life-years (DALYs) of any skin condition, which has a substantial influence on socioeconomic standing. Sick days are likely to increase, and academic performance is likely to suffer. Individuals diagnosed with AD have a higher likelihood of hospitalisation – more than twice as high as those without the condition (Eckert, 2018). Families with suffering children struggle financially because mothers have fewer work opportunities, less social support, and more anxiety. Parents must spend over one hour a

day on the offspring's eczema. Cost is a top stumbling point in low-income, single-parent households (Holm & Jemec, 2004; Lewis-Jones, 2006).

1.3 Diagnosis

AD diagnosis is based on clinical evidence. Physicians should take the patient's history, the distribution and shape of the lesion, and any related clinical symptoms into account when making the diagnosis. Several organisations have developed official guidelines. However, the sensitivity, specificity, and validity of recommendations for clinical investigations differ from their utility in real life (Eichenfield et al., 2014). Apart from pruritus and xerosis (abnormal dryness), different symptoms may dominate, depending on acuity. Common during acute exacerbations are erythema (skin redness resulting from increased circulation in superficial capillaries) and excoriations (physical signs of pruritus including oozing and eroding crust). Besides eczema papules and pruritic nodules, which are common signs of spongiosis (mostly intercellular oedema), the epidermis gets thicker and leathery (lichenification) when there is long-term inflammation (Hanifin et al., 2022; Saloga et al., 2006).

1.3.1 Diagnostic criteria

Among the major diagnostic criteria are the following: (1) Pruritus, (2) characteristic distribution and morphology: in adults - flexural lichenification and in infancy - facial and/or extensor involvement, (3) persistent or recurrent dermatitis, and (4) familial or personal history of atopy (AD, allergic rhinitis, asthma). These criteria, published by Hanifin and Rajka in 1980, remain the gold standard for diagnosing AD. The four criteria listed above are the major ones.

To be diagnosed with AD, one must fulfil at least three of them and additionally not less than three of the twenty-three minor criteria listed below: (1) Xerosis, (2) Severe hereditary or systemic xerosis, (3) Immediate (type 1) skin-test reactivity, (4) High serum IgE, (5) Onset at a young age, (6) Cutaneous infections, (7) Nonspecific foot/hand dermatitis, (8) Nipple eczema, (9) Lip inflammation, (10) Recurrent conjunctivitis, (11) Skin folds underneath the lower eyelids; Vision disorders: (12) Thin and irregular cornea and (13) Cataract of anterior lense, (14) Dark circles under the eyes, (15) Pale or red face, (16) Dry and pale patches on the face, (17) Necklines, (18) Pruritus when sweating, (19) Hypersensitivity to lipid solvents and wool, (20) Goosebumps, (21) Food hypersensitivity, (22) Psychological and

environmental factors (23) Elevation of skin when pressed or delayed redness after acetylcholine injection (Hanifin & Rajka G., 1980).

The criteria of Hanifin and Rajka, while comprehensive and frequently employed in clinical trials, might be challenging to apply in clinical practice. Furthermore, a number of the minor criteria are ambiguous or unusual. To overcome these restrictions, several international organisations have proposed adjustments. Epidemiologic studies commonly use the UK Working Party's criteria, wich consist of one mandatory and five essential criteria. The Joint Task Force and American Academy of Dermatology guidelines define AD as a chronic, pruritic-inflammatory disease primarily affecting paediatrics. Diagnosis is based on patient history, clinical findings, and exclusion of other dermatoses. To accomplish this, the American Academy of Dermatology suggests using skin biopsies to rule out other skin conditions.

AD diagnosis remains clinical due to a lack of biomarkers. Elevated IgE levels are associated with 20% of affected individuals. It is controversial to classify illness groups as „intrinsic" or „extrinsic" based on IgE elevation because it is still unclear what these variants include (Eichenfield et al., 2014). Furthermore, total IgE levels are not specific and shift with the severity of the condition, making them unreliable markers. They may also be higher in other diseases like cancer or autoimmune disorders (Arbes Jr. et al., 2005).

1.3.2 Severity scales

There are several different disease severity scales; the most widely used ones are the Eczema Area and Severity Index (EASI), Scoring Atopic Dermatitis (SCORAD) and Investigator's Global Assessment (IGA) (Chopra et al., 2017). The higher correlations between the EASI and SCORAD scales in comparison to IGA are due to similar factors, such as the severity and scope of symptoms. It is difficult to support any known outcome assessment because each measurement has its benefits and limitations. Whereas IGA is quick and easy, SCORAD is an appropriate and composite approach when many different clinicians assess one patient. There are already more than twenty different tools available to measure the severity of AD, and each one measures a different aspect of the disease. This makes it harder to improve evidence-based treatment. The Harmonising Outcome Measures for Eczema advised in 2014 that the EASI should be used in all trials to measure the severity of clinical symptoms associated with AD. The EASI's strong intra- and inter-rater reliability indicates it is appropriate for use in daily practice (Bożek & Reich, 2017).

1.4 Clinical guidelines

This chapter provides an overview of current clinical guidelines for AD, emphasising a stepwise approach that begins with basic non-pharmacological care. As needed, pharmacological treatments are gradually introduced and tailored to each patient's condition and response, with systemic therapies reserved for more severe cases and short-term use.

1.4.1. Basic care

Topical therapy is the cornerstone of treating AD, frequently combined with additional interventions to address various aspects of this complex illness. This section focuses on current recommendations for three popular non-pharmaceutical interventions: moisturisers, wet wrap therapy, and (bleach) baths (Wollenberg et al., 2022).

Therapy with medical moisturisers is the essence of all AD treatments. In mild diseases, moisturisers are the primary form of care; in more severe cases, they are a crucial supplemental therapy. Moisturisers can consist of emollients (such as glycol and soy sterols), occlusive agents (like mineral oil and petrolatum), or humectants (glycerol, urea, and lactic acid). Moisturisers improve skin barrier function and decrease transepidermal water loss. They help alleviate xerosis and other symptoms of AD: pruritus, erythema, fissuring, and lichenification. This means that anti-inflammatory drugs are not as necessary because of better disease control. Moreover, with sustained use (every three days, for instance), the flare-free intervals after remission could lengthen. That is why the guidelines suggest adding moisturisers to the routine of AD patients in periods of active disease, maintenance, and flare prevention. Moisturisers should be applied right away after taking a shower or bath and gently pat drying. Fragrances and sensitising ingredients should not be present in moisturisers, apart from that, trials show no superior moisturiser. The direct application on inflamed skin is usually poorly tolerated, and it is recommended to address the acute flare initially with anti-inflammatory approaches such as wet wraps (Eichenfield, et al., 2014b).

Wet wrap therapy may help people with moderate-to-severe AD lose less fluid during flare-ups and alleviate their symptoms along with topical corticosteroid treatment. Patients with oozing and erosive lesions, as well as paediatric patients, might first be treated with wet wraps before conventional topical treatment. Wet wraps can utilise topical corticosteroid creams and ointments. Using topical corticosteroids first, wet gauze next, and then another layer of dry gauze keeps the drug safe. Some professionals use two layers of clothes over

corticosteroids as an alternative. Apart from reducing water loss and acting as a barrier against scratching, wet wraps occlude and boost penetration of the medical product. However, caution is advised when using mid- to high-potency steroids due to restricted and transient but potentially systemic side effects (Eichenfield, et al., 2014b; Wollenberg et al., 2022).

Skin hygiene is crucial for managing AD. Generally, bathing is preferable to showering, particularly for young children. To mechanically remove crusts and bacterial particles in the event of superinfection, the skin needs to be completely washed, but softly and carefully. Cleaners either with or without antiseptics may be used. The therapeutic effect of antiseptics is short, and it is the mechanical effect of washing that is significant. Cleansing agents should be non-irritant and allergen-free, with pH values of about 5 to 6 (Wollenberg et al., 2022). A randomised study found no difference in bathing frequency between twice weekly and daily (Koutroulis et al., 2014). One study revealed no benefit from bath additives in regular care (Santer et al., 2018), while another indicated that some additives, such as oatmeal, dead sea salt, or natural oils, may improve benefits and lessen adverse effects (Maarouf et al., 2019).

The bleach bath, a method of eliminating bacteria and stimulating skin renewal, uses sodium hypochlorite, a powerful antiseptic. Salt concentrations exceeding 5% plus magnesium have been used in adults to mimic the effects of balneotherapy in the Dead Sea. Some researchers have questioned the effectiveness of antimicrobial bleach baths for moderate-to-severe AD patients with secondary bacterial infections (Chopra et al., 2017). Guidelines encourage the use of bleach baths for people with AD who have recurring bacterial infections throughout both the active and maintenance stages (Eichenfield, et al., 2014b; Wollenberg et al., 2022).

1.4.2 Topical pharmacological treatment

This section discusses topical anti-inflammatory therapies used in AD treatment, including topical corticosteroids, calcineurin inhibitors, and phosphodiesterase-4 inhibitors. When nonpharmacologic therapies fail, topical corticosteroids are the basis of anti-inflammatory treatment for both adults and children. Applied to acutely inflamed skin depending on circumstances (pruritus, insomnia, developing flare), topical corticosteroids are inflammation reducers. The choice of therapy depends on medication access, lesion location, and the tolerability of the agent. For acute control, moderate- and high-potency topical corticosteroids are advised, whereas low-potency ones are recommended for maintenance

therapy. The aim of therapy should be long-term disease control, prolonging the relapse-free period as much as possible, and minimising symptoms once eczema reduces in severity and itching subsides or goes away. Treatment with topical anti-inflammatory drugs can be either proactive or reactive. Reactive therapy treats lesional skin and ends once apparent lesions disappear. Proactive therapy with the aim of relapse prevention follows eczema healing and involves twice-weekly long-term treatment of often flared areas, together with daily use of moisturisers. The guidelines recommend using the fingertip unit method, especially on areas of thin skin like the face, neck, and skin folds due to potential adverse effects. Although topical calcineurin inhibitors can be used as maintenance therapy to avoid relapse, the guidelines advise using topical corticosteroids first to control a flare, and topical calcineurin inhibitors second to minimise cutaneous reaction intensity. Calcineurin inhibitors are the first-line treatment, especially for delicate locations where corticosteroid use is probably going to create adverse effects (or where it has already happened). As a new first-line treatment for symptom exacerbations and relapse prevention after long-term maintenance therapy, phosphodiesterase-4 inhibitors do not yet have any established criteria, as they have not been commercialised yet. JAK inhibitors are upcoming topical treatments – study results are encouraging. Though many are being developed, none of the JAK inhibitors have European licenses (Sidbury et al., 2014; Wollenberg et al., 2022).

1.4.3 Phototherapy

Taking into account variables such as accessibility, cost, skin type, and photosensitising medications, the guidelines suggest phototherapy for individuals with AD who do not respond well to topical therapies. UV phototherapy effectively relieves pruritus in AD, with narrowband ultraviolet B (UVB) and A1 (UVA1) being the most effective forms. Narrow-band UVB seems to be the best choice because of its efficacy, low-risk profile, and provider comfort. Aside from that, guidelines recommend UVB modalities for chronic AD, and photochemotherapy (PUVA, UVA combined with psoralen, a light-sensitizing compound allowing the radiation to penetrate deeper) reserved for those with significant widespread AD. Patients with persistent AD may also benefit from phototherapy as a maintenance treatment. Fitzpatrick skin type (phototype depending on melanin amount in the skin) and minimal erythema dose (UVB radiation dosage that causes noticeable erythema 24 hours after treatment), or both, may influence phototherapy dosage and frequency. In solid organ transplant recipients, long-term ciclosporin treatment raises the risk of photo-carcinogenicity. The simultaneous use of topical calcineurin inhibitors and phototherapy, just

as high sunlight exposure, should be avoided. There is a need for further research on the safety and efficacy of phototherapy in AD patients, as it is largely empirical and lacks evidence-based data (Sidbury et al., 2014).

1.4.4 Systemic treatment

When phototherapy or rigorous topical treatment is insufficient to deal with an adult's severe resistant AD, systemic medications may be recommended. The quality of life, age, sex, family planning, comorbidities, preferences, adverse effects, and costs all play a role. Before thinking about systemic medication, doctors should boost topical therapy, assess patients who do not respond well (differential diagnosis as well as triggering factors), and educate patients adequately to help them adhere to their treatment plans. To prevent flare-ups, the general strategy should involve an intense period of clearance with a topical corticosteroid, followed by a safe and personalised regimen of temporary topical corticosteroids, calcineurin inhibitors or emollients (Sidbury et al., 2014).

This section will discuss immunomodulating drugs, emerging treatments, biologic dupilumab, and systemic steroids. Previously, the only systemic treatments available for hard-to-address AD were broad-acting immunosuppressants. These included ciclosporin, systemic corticosteroids, azathioprine, enteric-coated mycophenolate sodium, mycophenolate mofetil, and methotrexate. The conventional use of these repurposed drugs for AD is considered off-label, with the exception of ciclosporin, which is licensed in at least fifteen European nations, Japan, and Australia (Wollenberg et al., 2022).

Patients with severe AD who are not responding to conventional therapy or who have a seriously impaired quality of life might consider systemic immunomodulatory drugs. Pharmaceutics commonly used include methotrexate, azathioprine, ciclosporine A, mycophenolate, prednisone, and dupilumab. Nevertheless, there is not enough data regarding the relative effectiveness of these rather broad-acting immunosuppressants, and rather than following strict rules, their use is determined by clinician and patient preferences. Ciclosporin improves severity scores by 55% after 6-8 weeks, what makes it the most efficient and safest immunomodulator. However, end-organ damage and cancer risk limit long-term use (no more than 1-2 years) (Wollenberg et al., 2022).

Biologics and small molecules are being examined in moderate-to-severe AD, including systemic biologics and both topical and systemic Janus kinase (JAK) inhibitors. JAK inhibitors are enzymes that transmit intercellular signals from cell surface receptors engaged

in several kinds of processes, such as inflammation and immune responses. As a number of hormone, growth factor, and cytokine receptor signalling pathways are involved in the inflammatory processes of AD, oral JAK inhibitors are a prospective therapy option because they can block these pathways (Schwartz et al., 2017).

Beyond the disturbance of inflammatory signalling in the skin, JAK inhibition has proven to reduce pruritus and enhance the integrity of the skin barrier by controlling filaggrin synthesis. Because consensus statements take time to analyse newly launched medications, most publications to date have included limited information on JAK inhibitors. Even though they are expensive, JAK inhibitros have shown great promise as a treatment by quickly reducing itching in people with moderate-to-severe AD with few side effects (Nakashima et al., 2022). When topical treatments are insufficient to control moderate-to-severe AD, patients might consider dupilumab, a disease-modifying biologic agent. One of the main causes of AD is a strong type 2 immune response activation, which is controlled by Th2 and innate lymphocytes and their cytokines IL-4 and IL-13. As the first biologic licensed for the therapy of moderate-to-severe AD, dupilumab is a reasonable approach to target these pathways (Tsoi et al., 2019). Despite the lack of comparison studies, it was the very first systemic biologic to treat AD in children older than 12 in the United States. Trials are underway for many more biologics for AD that target distinct cytokine signalling pathways. Tralokinumab and lebrikizumab are other monoclonal antibodies that have been recently approved by the European Medicines Agency for moderate-to-severe AD. The medicine inhibits IL-13 from interacting with its receptor, which lowers the amount of Th2 serum biomarkers in the blood and skin. Nemolizumab is an efficient anti-IL-31 monoclonal antibody, similarly improving pruritus and dermatitis related to AD (Wollenberg et al., 2021).

Due to their wide spectrum for inflammatory skin disease, systemic steroids are approved for adult and paediatric populations with moderate-to-severe AD; however, some guidelines do not recommend them due to a lack of safety and efficacy data. Particularly, recognised side effects and a relatively negative benefit-to-cost ratio appear to limit long-term treatment with these medications. Only in extreme circumstances, such as when beginning a new systemic therapy or treating a flare-up temporarily, should systemic corticosteroids be administered (Wollenberg et al., 2022).

Oral and topical antihistamines have limited data to support their usage. The guidelines recommend against using both non-sedating and sedating systemic antihistamines in general but allow occasional use of sedating antihistamines in patients whose pruritus is

causing their sleep to be disrupted. AD is a challenging condition for pregnant or lactating women, and so is the treatment. Pregnant women should avoid azathioprine, but under strict supervision, short-term steroids and ciclosporin are generally safe. There should be no use of methotrexate or mycophenolate mofetil (Langan et al., 2020).

The National Eczema Association states that there are currently (May 2025) thirty-nine injectable drugs, twenty-one oral medicines, and forty-nine topical medications for AD, some of which have innovative targets like stem cells produced from umbilical cord blood (National Eczema Association, 2025).

1.5 Whole-body cryotherapy

”Overall, the dermatologic literature supports WBC as a safe modality for the skin,” – states the Journal of Osteopathic Medicine (Kelly et al., 2023). In 2008, Klimenko et al. conducted the first trial for WBC on the AD population (2008). Because of its well-established anti-inflammatory and antioxidant properties, WBC is a very effective physical therapy form mostly applied in sports medicine to reduce pain, fatigue, inflammatory symptoms, and overtraining (Sadura-Sieklucka et al., 2019). It is also an adjuvant treatment for neurological conditions like multiple sclerosis, mental conditions including depression (Miller et al., 2011), metabolic conditions – in particular obesity (Varallo et al., 2022), and rheumatic conditions (Sadura-Sieklucka et al., 2019) such as arthritis, fibromyalgia, and ankylosing spondylitis (Stanek et al., 2018). Low temperatures induce a variety of advantageous physiological and biochemical responses in the human body. Up to now, it has been demonstrated that WBC may have a positive effect on inflammation (Stanek et al., 2018), oxidative stress (Miller et al., 2012), lipid profile (Saltykova et al., 2017), the endocrine system (Barłowska-Trybulec et al., 2022), skin (Skrzek et al., 2019) and sleep quality (Douzi et al., 2019).

To activate these effects, one must expose the human body to extremely low temperatures. Exposure to extreme cold stimulates cutaneous thermoreceptors, leading to stimulation of the thermoregulation centre in the hypothalamus. The increased heat production is directed by the posterior hypothalamus. This stimulation maintains a constant core temperature. Through both non-shivering and shivering thermogenesis in muscles and adipose tissue, the body controls its temperature upon exposure to cold. Elevated muscle tone and heat generation occur together with limited heat loss due to vasoconstriction and adjusted behaviour like changed posture or a rise in voluntary activity. Autonomous regulation, which is reflexive, prevents arbitrarily changing these multiple defence mechanisms. Thermal

tolerance is different in each individual and depends on a variety of factors such as age, hormone levels, body size, composition, and others (Sherwood, 2010; Gunga & Steinach, 2013). The drop in skin temperature sets off one of the most well-known physiological reactions to cold exposure. It triggers cutaneous receptors and their sensory afferents, which in turn stimulate sympathetic adrenergic fibres and cause distal venules and arterioles to constrict. As a result, there is less blood flow to the inflamed tissues, which slows down local metabolism and lessens the level of inflammation and the development of oedema (Paddon-Jones et al., 1997).

WBC exposes individuals in underwear to extreme cold for up to 3 minutes and stimulates the autonomic nervous system (Polidori et al., 2018). A one-person cabin (cryosauna) enables a systemic treatment, additionally eliminating direct contact with the cold agent for severe skin lesions on the face and neck. Direct contact with the nitrogen vapour in the open tank demands safety precautions because of the risk of suffocation. The gas temperature during the procedure varies from -100 to -175°C and decreases with each exposure, depending on the individual's cold tolerance. Woolen shoes and gloves protect vulnerable body parts. Although cryotherapy is a widespread treatment, standardisation of protocols is still lacking (Bouzigon et al., 2016).

An impaired hydrolipid barrier makes the skin of AD patients dry. In two studies on cryotherapy (Kepinska-Szyszkowska et al., 2020; Klimenko et al., 2008), the hydration of the epidermis improved after initial treatments, and a long-lasting effect was reported as well. The cryotherapy positively affects skin moisture and sebum levels, according to the study by Kang (2013). The skin becomes more hydrated the more lubricated it is (Boer et al., 2016). It was also noted that sebum production rose noticeably, correlated with increased skin moisture following WBC (Kang et. al, 2013). As observed in the research of Skrzek et al, WBC treatments do not influence the pH of the skin (2019). Lambers et al. showed in their study that the greater the harm to the skin, the higher pH value is required, as the acidic milieu must exist to begin with the development of the protective lipid barrier (2006). Also in another study (Misiorek & Szyszkowska-Kępińska, 2021), there was no noticeable change in pH levels, which again clarifies that cryotherapy does not appear to impair the skin's protective lipid barrier. The positive effect on epidermal hydration may be caused by the anti-inflammatory and anti-oxidative stress effects of WBC (Stanek et al., 2020).

Strong correlations link AD to its impact on stress response and disruption of autonomic body processes, often leading to exacerbations. An overly high parasympathetic tone that means that body cannot handle stress and an overly high sympathetic reactivity are two signs of AD, a stress-responsive condition (Yosipovitch et al., 2010). The results of the research demonstrated that a single 3-minute cryotherapy session elicits a robust autonomic response. Rising plasma levels of norepinephrine, elevation of blood pressure and heart rate variability indicate raised sympathetic activation and parasympathetic regulation of heart rate (Hausswirth et al., 2013). Low temperatures affect the metabolic rates as well as the muscular, neurological, endocrine, and circulatory systems. Therefore, researchers may use them to treat diseases that arise from these systems (Piotrowska et al., 2021; Skrzek et al., 2019). Research indicates that cryotherapy might decrease neutrophil migration and necrosis of cells, as well as slow down the velocity of nerve conduction and cell metabolism. These effects can ultimately lessen pain perception and subsequent tissue damage (Wilcock et al., 2006). Because it reduces inflammation and itching and has an effect on the nervous system, cryotherapy may help with long-term care for AD (Kepinska-Szyszkowska et al., 2020).

1.6 Osteopathic manipulative treatment

Osteopathic medicine and dermatology place a strong emphasis on the value of physical contact, especially palpation, in the diagnosis and treatment of skin conditions. OMT can improve the treatment of a variety of dermatological problems with the therapists' hands as essential diagnostic instruments (Ventura & Soti, 2024). Dermatologists identify skin manifestations of internal conditions, aiding early diagnosis and therapy. It might be possible to connect body structure and function by using noninvasive OMT techniques that target the physiology behind certain diseases. Osteopathic medicine builds on this structural and functional approach by recognising the patient as a self-regulating, integrated whole—body, mind, and spirit—which is especially important in understanding and treating chronic inflammatory skin conditions (Campbell et al., 2011; Giesey et al., 2020).

1.6.1 Person as a unit

Research on chronic inflammatory (skin) conditions demonstrates the powerful mind-body-spirit connection and how it can have a substantial effect on an individual's health. An outstanding example of this is AD (Patel et al., 2019). In a 2020 study, Hosono et al. discovered that myofascial release helped AD patients who were resistant to corticosteroids

with their pruritus, perhaps as a result of less psychological stress (Hosono et al., 2020). Stress can profoundly affect the appearance of the skin, thus making it a critical factor in addressing skin disorders. Targeting certain body parts impacted by stress, including the shoulders, neck, and scalp, may be utilised in the treatment. This could make it possible to regulate individuals' levels of anxiety, leading to more thorough patient care and improvement of the disease management (Ventura & Soti, 2024).

1.6.2 Capability of self-regulation

The human body possesses a remarkable capacity for self-regulation and healing. It may rebuild itself, fix abnormalities, and accelerate development in response to its needs. Similar to AD, several skin conditions have an immune component in their aetiology. We can use OMT to address immune system dysfunction (Campbell et al., 2011). Osteopaths are able to develop individualised treatment regimens that target the root causes of skin issues. OMT might reduce relapses and lessen the need for potentially harmful drugs (Ventura, 2024).

1.6.3 Structure-function interrelation

The skin, as the body's biggest organ, exemplifies the complex interplay of structure and function. Several cutaneous conditions are caused directly by an impairment in skin structure, which results in inappropriate skin function. A deficiency in filaggrin causing AD, leads to dry, sensitive skin with impaired function (Campbell et al., 2011). Because osteopathic practitioners are aware of how the body components are interconnected, they are able to evaluate and treat medical conditions in an all-around manner (Ventura, 2024).

Osteopathic practitioners treating patients with dermatological conditions prioritise individual patient care. In order to prevent future skin problems, they emphasise preventive treatment by targeting imbalances underneath the dysfunctions. They promote general wellness and teach patients self-care techniques and lifestyle modifications that will help them keep healthy skin (Ventura, 2024). Dermatology is a medical speciality that uses a comprehensive history and physical examination to diagnose and treat patients, emhasising the importance of tactile sensations and understanding the osteopathic principles (1. the person as a unit; 2. the capability of self-regulation and self-healing; 3. structure-function interrelation) (Campbell et al., 2011; Giesey et al., 2020).

1.6.4 Expertise in lymphatic pump techniques

Somatic dysfunction is a metabolic change that affects tissue function and homeostasis, often lasting over time. Palpation can identify somatic dysfunction, which can progress to tissue fibrosis and sclerosis. Restricted range of motion is a defining feature of somatic dysfunction, qualitative and quantitative alterations in a joint or tissue area. Laboratory research has shown that indirect manual methods may be able to heal tissue, especially connective tissue, by making growth factors and cytokines that lower inflammation (Parravicini & Bergna, 2017). Nevertheless, the literature lacks solid proof of OMT's effectiveness treating inflammatory conditions, maybe as a result of its dependence on reference values – regular blood tests do not reveal elevated inflammatory markers in somatic dysfunctions, as it is an example of low-grade inflammation (Verzella et al., 2022). Dery et al. was the first one to observe the impact of lymphatic pump technique on the lymphatic function, despite its long history in osteopathic schools. Dery's et al.'s investigation on rats (2000) was followed in 2005 by a study of Knott et al. (2005) who demonstrated that thoracic lymphatic pump technique improves thoracic flow rate in dogs. The 2012 study of Schander et al. was the first to document how lymphatic pump technique affects the lymphatic system's inflammatory mediator flow and concentration. It finds that although lymphatic pump techniques do not substantially raise cytokines, they do enhance lymphatic flow, which in turn increases the outflow of inflammatory mediators from the tissue into blood (Schander et al., 2012).

Through both external and internal pumping mechanisms, the lymphatic system moves lymphatic fluid from the interstitium into the central circulatory system. Tentorium cerebelli, thoracic inlet, and abdominal and pelvic diaphragms are the functional diaphragms that contribute to lymphatic return. In the pelvis and thorax, the diaphragms are external pumps that work by contracting the muscles that surround lymphatic vessels. Intrinsic forces include sympathetic innervation that stimulates the lymphatic vessel contraction and spontaneous contractions of the major lymphatic vessels' smooth muscle walls. The proper operation of the lymphatic pumping system in segmentally connected body regions can be reflexively impacted by abnormally altered autonomic activity (Hruby & Martinez, 2021). Because the decrease in lymphatic drainage results in an accumulation of inflammatory agents in the epidermis, lymphatic dysfunction may also contribute to pruritus (Giesey et al., 2020).

1.6.5 Treatment protocol

Precise treatment goals should aid in developing guidelines for the treatment of AD (and other inflammatory skin conditions). A treatment protocol makes a methodical approach possible. As a rule, therapy starts with the most central lymphatic system parts before moving on to the more peripheral ones. The initial lymphatic treatment involves opening diaphragmatic restrictors to allow distally mobilised fluid to flow back to the heart (Giesey et al., 2020, Hruby, 2021). The following are the guiding concepts of this strategy: initial treatment of the supraclavicular fossae, addressing any limitations in the main pumps – body's diaphragms, myofascial release across lymphatic routes, and relief of clogged lymph nodes (Hruby, 2021).

To detect somatic dysfunction and its impact on the lymphatic system, a thorough history and physical examination are crucial. Any signs of tissue trauma, inflammation, and puffiness or swelling should receive particular attention. The changes in tension, tenderness, or full, soggy tissue texture at the sites of terminal lymphatic drainage are especially helpful in identifying whether there is a tissue congestion. Fascial limitations may inhibit lymphatic flow. Fluid pumps in membrane- and myofascial-based regions, including tentorium cerebelli, cranial dura, supraclavicular fossa, thoracoabdominal diaphragm, and pelvic diaphragm, govern restricted motion. Somatic dysfunctions in the spine and rib cage can decrease lymphatic flow; therefore, it is necessary to palpate the interstitial tissues for extra fluid and congestion in order to identify locations that might benefit from pump techniques (Hruby, 2021).

The flare' location dictates the targeted treatment region. Lesions on the neck, face, and scalp can be treated by releasing tentorium cerebelli. Thoracic inlet treatment improves outflow from the head and neck. When the thoracoabdominal diaphragm relaxes, it may help the lymph move into and from the upper back and chest. When the pelvic diaphragm is treated, lymph flows more freely to the lower back, abdomen, pelvis, and buttocks. For somatic dysfunctions in lower and upper extremities, we can treat the plantar and palmar fascia (Leone et al., 2018).

Through the modification of muscle tone, the release of myofascial limitations, the modulation of neural reflexes, the maintenance of a balance autonomic tone, and respiration, OMT treatments can improve the function of the lymphatic system. Improving the lymphatic flow enables relief of the symptoms in the congested areas. Lymphatic pump

techniques improve the immune system by increasing lymph flow and spreading immunological mediators (Hruby et al., 2021).

The lymphatic approach is absolutely contraindicated in cases of coagulopathy, persistent infections, and conditions that have the potential to reactivate, like tuberculosis. Active malignancy is one of the relative contractions because it is unclear if lymphatic OMT may mobilise cancerous cells (Leone et al., 2018).

1.6.6. Preferred techniques

In the management of AD, supporting the lymphatic system is a key therapeutic goal. Osteopathic manual techniques aim to release fascial restrictions, improve circulation, and reduce inflammation. Fascial strain can cause end resistance by obstructing thoracic inlet, the lymph end point. Myofascial release is a important step in fixing lymphatic drainage because congestion in this area can cause end resistance to lymphatic flow, even if other areas are fine (Hibler et al., 2014). Myofascial release has been found to promote tissue flexibility, improve circulation in fascial layers and oxygenation, along with enhancement of the immune system locally (Leone et al., 2018). In places where there is tissue congestion, manipulative treatment like raisning the ribs can help move medicines around, speed up the healing process, and get the body's natural system working again (Hibler et al., 2014). A soft-tissue technique called effleurage uses mild strokes to treat superficial patches and plaques. Leone et al. suggested that AD patients use this method at home when applying moisturisers (Leone et al., 2018). Below the manual techniques recommended for individuals with AD:

Table 1: *Recommended Manual Techniques for Atopic Dermatitis*

Thoracic inlet release	the fourth and fifth fingers are positioned between the first rib and clavicle, while the thumbs are positioned on the processus transversus of the second thoracic vertebra and the second rib's head; up until the tissues are released, the thoracic inlet is moved either directly or indirectly (Giesey et al., 2020)
Effleurage	in order to promote lymphatic and venous return, the clinician rotates fingers/ palm from the distal to proximal tissue (in the direction of the heart) (Giesey et al., 2020)

Rolling	Rolling movement along the treatment plane entails rising the skin apart from the underlying fascial layers (Leone et al., 2018)
Pedal pump	the clinician uses a rhythmic pumping action on both feet in a supine position (Giesey et al., 2020)
Myofascial release	The clinician guides tissue along the route of least resistance up until relaxation is accomplished or forces the tissue to a stage of maximum restriction (indirect or direct application); constricted fascia is helped to relax (Hibler et al., 2014 & Leone et al., 2018)
Rib raising	The clinician encourages caudal motion while applying gradual, deliberate pressure to the rib angles laterally and anteriorly (direct application) (Hibler et al., 2014)
High velocity low amplitude	A joint is carried past the restricting barrier within the physiological range of motion by an abrupt force (thrust) (Hibler et al., 2014)
Muscle energy	After the patient is positioned within the restricted barrier, the patient actively engages the muscles for about five seconds against the clinician's counterforce (Hibler et al., 2014)
Diaphragm release	By using pressure, disengagement, and the entire breathing cycle, the clinician palpates the diaphragm and notes any restricted areas, unwinding the fascia (keeping the tissue moving in the direction that allows the most freedom (Leone et al., 2018)
Lymphatic technique for cubital fossa	Starting from the wrist, the clinician applies pressure with the thumb on the extensors and with the fingers on the flexors and moves proximally (Leone et al., 2018)

It has been demonstrated that OMT improves the immune system and helps restore autonomic function, both of which improve an individual's health. Osteopathic practitioners can improve patient care by using direct as well as indirect manual techniques to heal somatic dysfunction and return the body to its normal physiological function. Since manual therapies have been demonstrated to change the lymphatic flow and inflammatory agents, using OMT may help resolve a pathologic state (Hibler et al., 2014).

2 Research design and method

To the best of my knowledge, no comparable study has been conducted yet. Due to the explorative character of the research, it aims to get preliminary data on the effectiveness of these two approaches. The second goal is to gain expertise that might be significant for similar research projects in the future.

2.1 Research question and hypotheses

This study tries to answer the question: Is there a significant difference between the effects of OMT and WBC on patients with AD regarding disease severity?

Null hypothesis: There is no significant difference between the effects of OMT and WBC on AD in terms of disease severity.

Alternative hypothesis: There is a significant difference between the effects of OMT and WBC on AD in terms of disease severity.

2.2 Study design

This study is an open randomised controlled clinical trial. The study took place in a private physiotherapy and osteopathy practice located at Kremstalstrasse 53, 3500 Krems an der Donau, Austria from September 2023 to December 2024. The participants were informed about the study's design, anonymity, and the possibility of withdrawal at any time before they gave their written agreement. The study was conducted in accordance with the Declaration of Helsinki. Wiener Schule für Osteopathie authorised the scientific approach of the project. The flowchart on the following page outlines the study protocol, including participant allocation and key intervention steps.

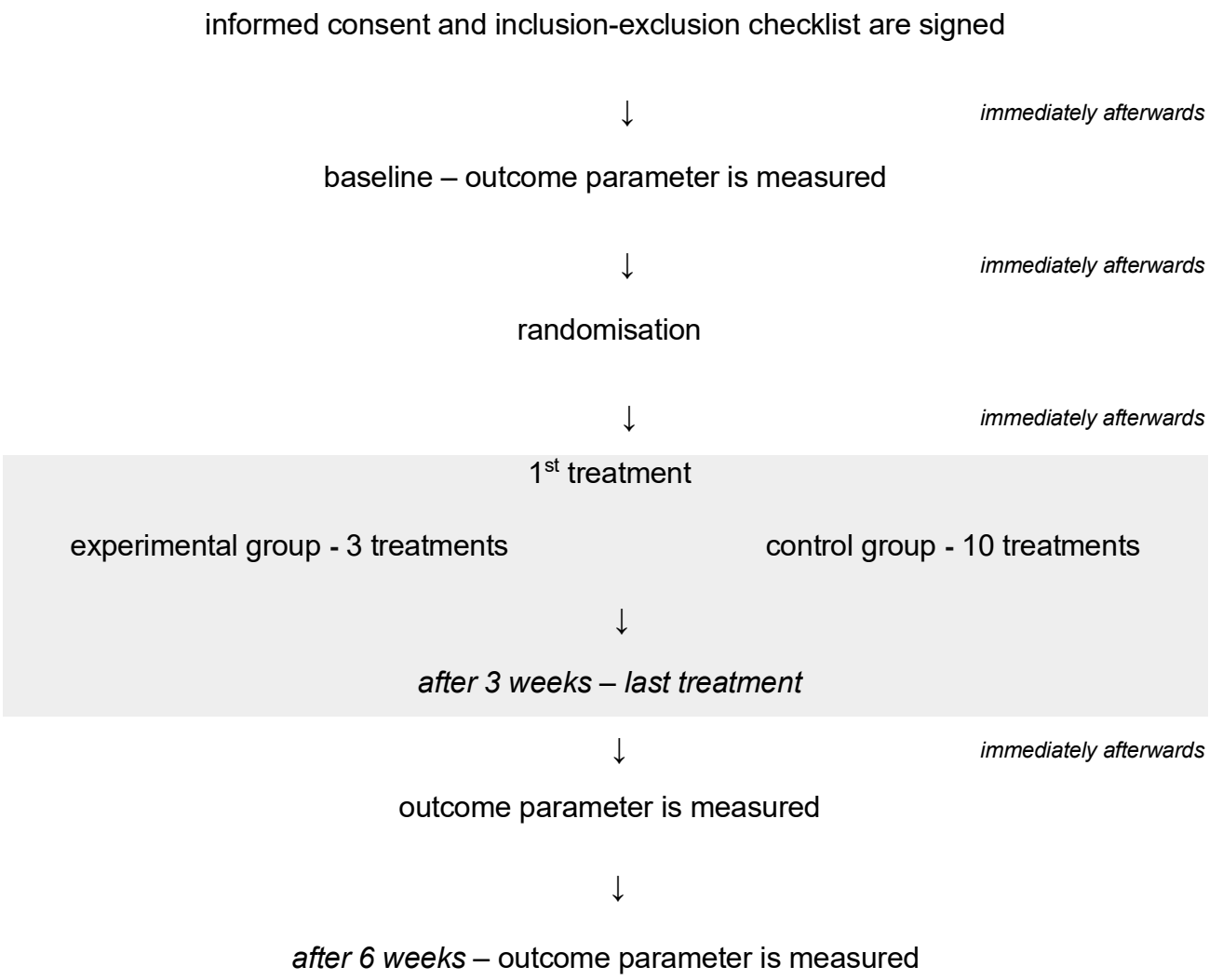

Figure 1: *Flowchart illustrating the study protocol*

2.3 Recruitment

Fifteen people with AD were recruited through word-of-mouth, flyers left at pharmacies, and social media postings. From fifteen recruited individuals, twelve fulfilled the inclusion criteria and had been enrolled. Just after the allocation to the experimental group, one person left the study because the control group treatment only was the motivation to participate.

2.4 Randomisation

Following enrollment, participants were randomised using a block randomisation with a block size of 2. To reduce waiting time, two participants were scheduled simultaneously, and randomisation was conducted by coin toss. Short waiting time potentially improved retention rates and participant compliance. Since the study already excluded individuals with multiple comorbidities, no match control was required.

2.5 Procedures

Participants in the control group underwent a series of WBC sessions over three weeks. The experimental group received three individualised osteopathic treatments applied within a non-standardised, black-box approach.

2.5.1 control group: whole-body cryotherapy

This study used the Cryosauna Cryomed Mini, which operates on fluid nitrogen. Once pre-cooled, the participants entered the cabin. The appropriate height of the standing platform inside of the device was set by an elevator, so that the shoulders were still exposed to the nitrogen, but the head was outside, so that there was no risk of suffocation. Since 2022, the therapy practice has a storage agreement for the Cryomed Mini cryocabin in a ventilated, separate room with an independently supplied alarm system. Medical professionals watched over each session the entire time. Woolen shoes and gloves protected vulnerable body parts.

During the first session, liquid nitrogen was used to cool the device down to -100 degrees Celsius, and later, it was cooled down to -120 degrees Celsius. Except for the initial treatment, which lasted only one minute, the WBC sessions lasted three minutes. As there are no definite guidelines on the duration and the temperature during the cryotherapy session, an assumption of the treatment protocole was made based on the published studies (Doets et al., 2021; Kepinska-Szyszkowska et al., 2020):

Initial treatment:	-100°C for 1 minute
Treatments 2-10:	-120°C for 3 minutes

However, the cold exposure was not tolerated well enough by two participants, and the exposure time was individually adjusted.

Adjusted treatment (2-10) for 2 from 5 participants:	-100°C for 2 minutes

2.5.2 experimental group: OMT

Each individual from the experimental group received three osteopathic treatments, performed within a black-box protocol, each of which took about 60 minutes. Within the first treatment, an anamnesis and a thorough osteopathic assessment were made. Regarding the methodology, the respiratory-circulatory model was applied to all of the participants, but

also the metabolic, neurologic, and biomechanical approaches were relevant. All five individuals had visible signs of lymphatic congestion in the thoracic outlet. In four out of five individuals, a global dysfunction of Th10 – L1 was found. All five participants suffered from AD since early childhood; two of them experienced exacerbation of symptoms again in the puberty. Four had other atopic conditions, such as asthma, rhinitis, and conjunctivitis, one had an allergy aside from the atopic spectrum. Two were coping with food intolerance and diarrhea, and one had gastro-esophageal reflux disease. The affected sides were most commonly upper extremities' flexors (elbows, axial cavities) and lower extremities (knee cavities, inner thighs, and calves). Two individuals had lesions in the face, neck, and back, and one in the nipples. The table below presents the individual approach for each participant.

Table 2: *Overview of Individual Osteopathic Approaches and Interventions Among Study Participants*

Indivi-dual No.	Osteopathic Models	Main Findings	Treatment
2	Respiratory-circulatory + biomechanical	• global dysfunction Th10 – L1 • lymphatic congestion in the thoracic outlet • sacroiliac joint dysfunction	- thoracic inlet release - thoracolumbar fascia release - pelvic release - Th12/L1 lumbar roll - C7/ Th1 mobilisation - neck fascia release
3	Respiratory-circulatory + metabolic-energy	• visceral (liver, stomach, duodenum, radix mesenteri, adrenal gland) dysfunction • lymphatic congestion in the thoracic outlet • cranio-sacral dysfunction	- diaphragm release - liver pump - release of visceral dysfunctions - rib rising - cubital fossa release - tentorium cerebelli release
6	Respiratory-circulatory +	• global dysfunction Th10 – L1 • lymphatic congestion in the	- thoracic inlet release - sternum recoil - cisterna chyli pump

	neurologic	thoracic outlet • lung dysfunction	- C0/C1 mobilisation - neck fascia release - pedal pump
7	Respiratory-circulatory + metabolic-energy	• lymphatic congestion in the thoracic outlet • lymphatic congestion in the mediastinal area • global dysfunction Th10–L1	- CV4 - GOT rib cage - rib rising - effleurage nipples area - neck fascia release
10	Respiratory-circulatory + neurologic	• global dysfunction Th10–L1 • lymphatic congestion in the thoracic outlet • cranio-sacral dysfunction	- thoracic inlet release - diaphragm lymphatic pump - C0/C1 mobilisation - CV4 - sacral bone release - pedal pump

2.6 Blinding

It was not possible to blind the participants or the therapist who provided the interventions. The individuals receiving OMT received more time and attention during each treatment, while the control group showed up almost three times more frequently. With the potential sources of bias in mind, this study rejects the meaningful role of blinding (Moustgaard et al., 2020).

2.7 Outcome measures

The primary outcome measure was the severity of clinical symptoms associated with AD. The self-administered Eczema Area und Severity Index (SA-EASI), a validated scale (R = .62) (Housman et al., 2002) was used. Participants filled out the forms in the digital form on the tablet or on their own mobile devices (dermatools.net). There were three assessments during the trial. The assessment was conducted before the first osteopathic treatment, after the tenth osteopathic treatment, and three weeks later at the follow-up. The SA-EASI results are presented with a 0-72 points scale and are to be interpreted as follows:

<1	almost clear
1.1 – 7	mild symptoms

7.1 – 21	moderate symptoms
21.1 – 50	severe symptoms
51 – 72	very severe symptoms

For each of four body regions (head and neck, trunk, upper extremities, and lower extremities), the participants estimated the area of involvement using their palm surface. Five signs of AD (erythema, oedema/papulation, excoriation, pruritus and lichenification) were assigned an intensity level as well. They had to mark the scores on visual analogue scales. To be more precise in the clinical practice, SA-EASI delivers four corresponding outcome measures. The following is a list of measures where the Visual Analogue Scale (VAS) was used to assess erythema, lichenification, and pruritus, while Body Surface Area (BSA) represents the percentage of skin affected by lesions.

acute SA-EASI (0-72)	sum of VAS (erythema + lichenification + pruritus)	
total SA-EASI (0-96)	chronic SA-EASI + acute SA-EASI	
chronic SA-EASI (0-24)	VAS excoriation * 0,04 * BSA	
affected BSA	number of palms / 100 x 6	(Hanifin et al., 2022)

All four outcome measures (called later on: „acute AD", „total AD", „chronic AD" and „surface AD") were evaluated to interpret the results in this trial.

2.8 Unplanned events

After the second cryotherapy treatment, one participant withdrew from the study due to acute breathing difficulties, despite the session lasting only 60 seconds. As mentioned earlier (see 3.2. Recruitment), another participant left the study immediately after being allocated to the experimental group, as their primary motivation for participation was receiving the control group treatment. In the case of the participant who experienced breathing difficulties, cryotherapy was also the preferred treatment. It is likely that due to communication issues in German, information about the participant's chronic respiratory conditions (including several pulmonary infarctions and heart failure) was not revealed in the health history questionnaire. There was one more unplanned event in the control group: at the ninth

cryotherapy session, the participant seemed suddenly disoriented. Fearing unconsciousness, the operator opened the cabin's security door for approximately 10 seconds. After this precautionary manoeuvre, it was possible to continue the treatment in an ordinary manner. The participant was on an empty stomach, did not drink anything, and woke up just about 30 minutes prior to treatment, which presumably explains the limited stability of the participant that day.

2.9 Eligibility criteria

Inclusion criteria were AD diagnosis in the past and symptoms for at least twelve months before entering the trial, age between 18-70 years, and no contraindication to WBC sessions. Individuals with clinically unaffected skin could also participate, as intact-appearing skin is not a proof of health due to AD flares (Tang et al., 2014). The maximum age limit was determined by the safety of WBC in terms of unintended BP changes (Missmann et al., 2016). The fulfilment of inclusion criteria was defined through AD diagnosis in past medical history and answering the health history questionnaire.

Lack of an informed consent for research, as a lack of proof of a voluntary, informed decision to participate (or refuse to participate in the trial), would have been the main criterion to exclude from the trial (Cahana et al., 2008). Given the lack of evidence regarding the safety of cryotherapy for pregnant and breastfeeding women, the pregnant women and breastfeeding mothers could not participate. Because exposing an open wound to extremely low temperatures can lead to further tissue damage, delayed wound healing, and increased risk of infection, no individuals with open wounds were accepted (Lubkowska, 2012). The presence of diseases that are prohibited by whole-body cryotherapy, such as Raynaud’s disease, varicose veins, thrombotic and inflammatory disorders of the veins, neoplasm, serious dysfunctions of the circulatory system, uncontrolled hypertension and hypothyroidism, neuropathies, significant anaemia, acute and chronic illnesses of the respiratory system, etc., were all covered in the health history questionnaire. To minimise the risk of complications and ensure the safety of the participants, individuals suffering from these conditions could not participate, as well as patients during or after immunotherapy due to potential adverse effects and interference with the immune system (Lubkowska, 2012). The lymphatic approach, as a part of the OMT, is absolutely contraindicated in cases of coagulopathy, persistent infections, and conditions that have the potential to reactivate, like tuberculosis. Also, these conditions belonged to the exclusion criteria (Leone et al., 2018).

To avoid the ethical and practical challenges associated with involving children, individuals under the age of eighteen were excluded from participation (Panacek & Thompson, 2007). In order to make sure that the study population is clear and that the outcomes that were measured are only related to AD, conditions like Netherton's syndrome, severe contact dermatitis, chronic solar dermatitis, and others that cause inflammation on the skin were not allowed. Patients receiving immunosuppressive systemic medications, oral or topical corticosteroids, and other therapies expected to be beneficial for AD (like psychotherapy, phototherapy, etc.) in the recent six weeks were excluded as well. This limitation was put in place to make sure that results that were measured were directly linked to the treatments in both groups (osteopathy and cryotherapy) (Panacek & Thompson, 2007). Because of poor retention and greater difficulty maintaining contact with participants, and in consequence weak adherence rates, people with severe mental or organic conditions as well as alcohol or drug abuse were also excluded from this clinical trial.

2.10 Early termination

Potential reasons for terminating the entire trial included difficulties with recruitment or participant retention (e.g., fewer than six participants enrolled after one year), insufficient resources (e.g., nitrogen supply failure or serious illness of the therapist), and concerns regarding participant safety (e.g., unexpected adverse events or ventilation system malfunctions).

Reasons for discontinuing the trial for an individual participant included the need to prevent further harm in the event of a serious adverse reaction directly linked to the intervention, noncompliance (e.g., engaging in risky behaviour or missing scheduled visits), or personal circumstances such as illness, pregnancy, or family emergencies.

2.11 Sample size

With G*Power 3.1.9.2 software it was possible to calculate the number of participants summed over both design groups. In the study used for sample size calculation (Zhong, 2021) an effect size of RR = 1.25, p = 0.005, I^2 = 82% was stated. The risk ratio of 1.25 was transformed into Cohen's f ratio of 0.625. When f is zero, it signifies that all population means are even, whereas a ratio bigger than 0.4 means a large effect size (Metsämuuronen, 2024). To plan the analysis using a mixed ANOVA with a significance level of 5%, a power calculation was conducted. It showed that a total sample size of 8 would yield 90% power

to detect a large, standardised effect size of 0.625. Assuming a 20% dropout rate, the goal was to enroll 5 individuals in each group.

2.12 Statistical analysis

All statistical analyses were performed independently by the author using Jamovi 2.3.28 software. The analyses included descriptive statistics, assumption checks, and mixed-design ANOVAs as appropriate for the study design. Since simulation studies have shown that mixed ANOVA is relatively robust against violations of the normality assumption, no transformations were made (Glass et al., 1972). The outliers were not excluded to the sample size regarding loss of power. For one variable that violated normality assumptions, a non-parametric test was applied instead.

3 Results

This chapter presents the results of the analyses conducted to assess the effects of the interventions on AD. The first section outlines the descriptive characteristics of the sample, while the second presents the results from the repeated measures ANOVA.

3.1 Sample Descriptives

Ten individuals with mild-to-moderate AD participated in the trial, including seven females and three males, aged between 22 and 66 years. The control group consisted of four females and one male, while the experimental group included three females and two males.

BMI was approximately normally distributed for the experimental group but not for the control group. The height ranged from 161 to 181 cm, and the weight was between 55 and 88 kg. Seven participants had a normal weight, two were overweight, and one was underweight. All three participants out of the normal BMI range were allocated to the control group; the one with underweight was the outlier. The age was normally distributed.

Table 3: *Descriptive Statistics and Normality Test Results for Age and BMI by Group*

			Shapiro-Wilk	
	group	**Mean**	**W**	**p**
age	control	40.6	0.778	0.053
	experimental	25.6	0.981	0.940
BMI	control	21.5	0.638	0.002
	experimental	25.0	0.962	0.819

Both the control and experimental groups consisted of 2 individuals with mild (EASI total score between 2.3 – 6.2) and 3 with moderate AD symptoms (EASI total score between 7.4 – 16). Baseline severity distribution is presented in the table on the next page.

Table 4: *Baseline EASI Total Scores by Group*

group	Mean	Median	Minimum	Maximum
control	8.18	7.40	2.30	16.0
experimental	8.32	7.80	3.60	14.8

3.2 Repeated Measures ANOVA

Four outcome parameters were analysed: EASI acute, EASI total, EASI chronic, and EASI surface. A repeated measures ANOVA was conducted for each parameter to evaluate changes within and between groups across three time points. Non-parametric alternatives were applied only to the EASI surface, as the assumption of normality was not met.

3.2.1 EASI acute

A mixed-design ANOVA was conducted to compare acute EASI scores between the control and experimental groups over time. Acute0 refers to the baseline acute EASI score, while acute1 and acute2 represent the second and third measurements, respectively.

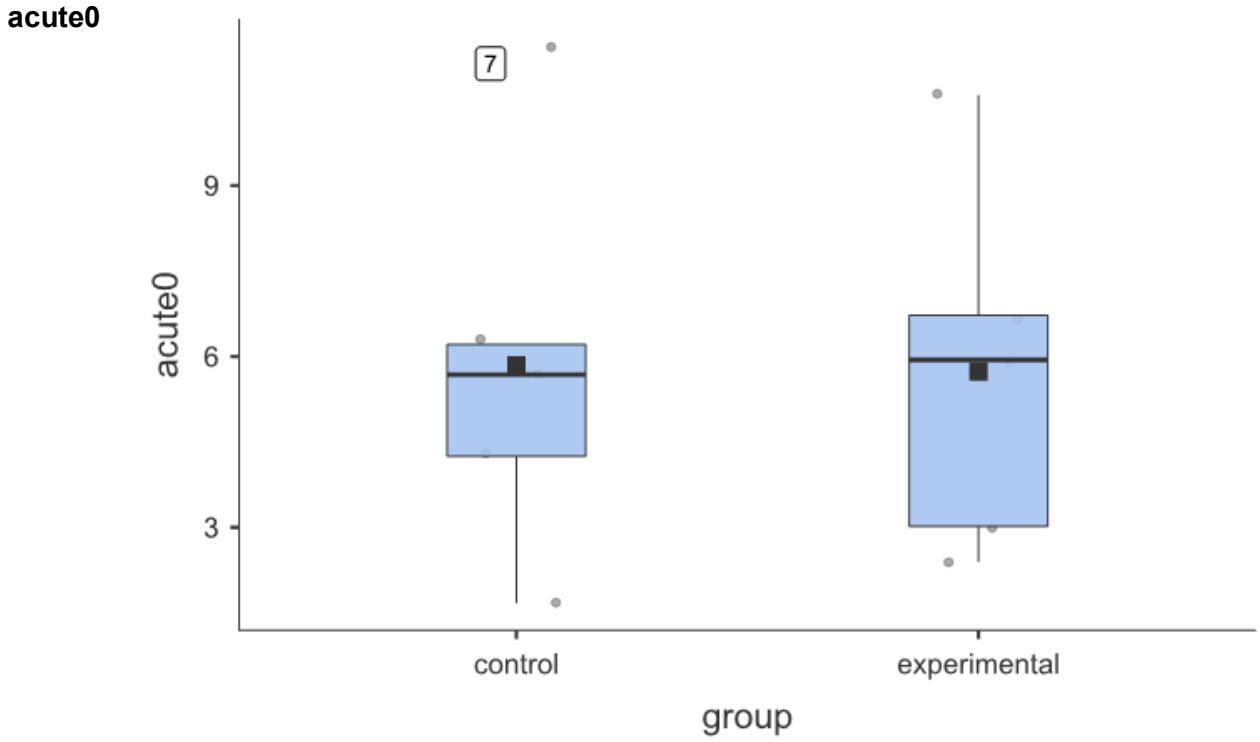

Figure 2: *Acute EASI Scores at Baseline (acute0)*

Both groups showed similar median acute EASI scores at baseline, around 6. The horizontal line indicating the median and the black square representing the mean in the box plots were similar, which implies the data in each group were relatively evenly distributed.

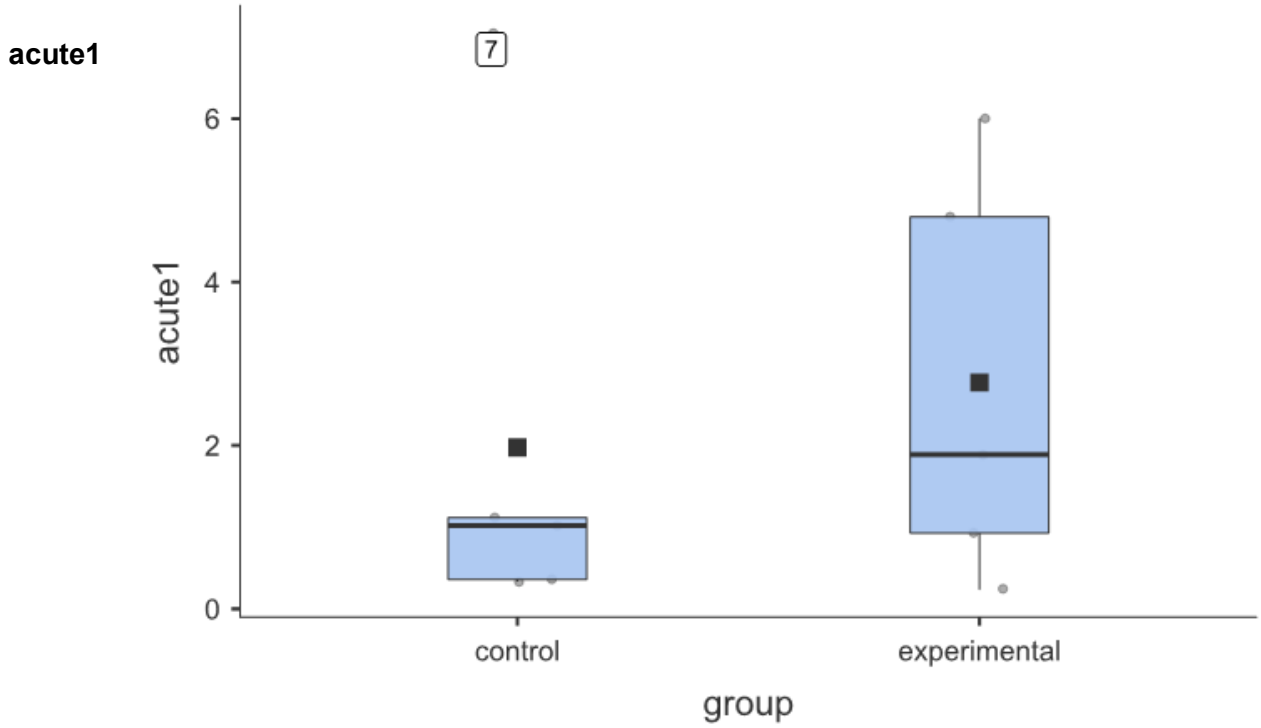

Figure 3: *Acute EASI Scores after the Last Treatment (acute1)*

Figure 3 displays the acute EASI scores after the 3-week treatment period. The mean scores are close to the medians in both groups. The control group showed a low median score, with a narrow interquartile range and minimal variation among participants. The experimental group demonstrated a wider range of scores. Compared to the baseline, both groups showed reduced EASI scores following treatment.

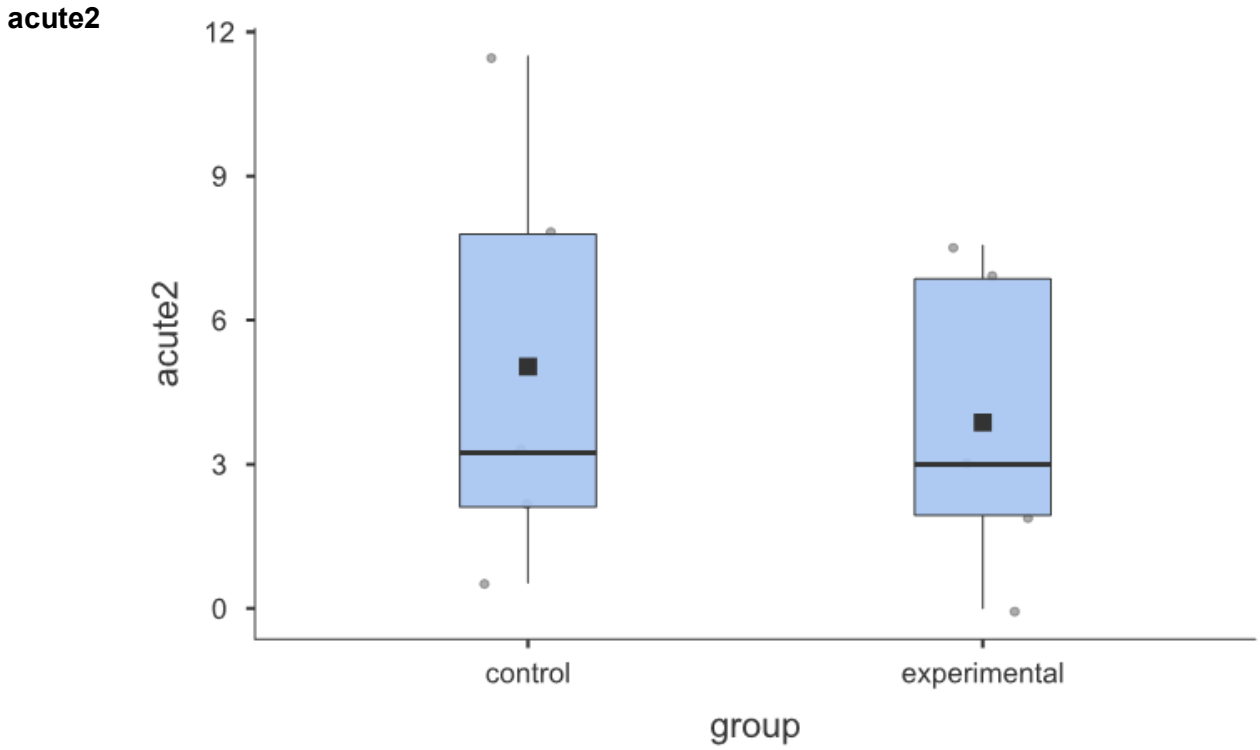

Figure 4: *Acute EASI Scores at the 6-week follow-up*

Figure 4 shows the acute EASI scores at the 6-week follow-up. The distribution in both groups is relative wide, the means in both groups are comparable. In both groups, the EASI acute scores at follow-up (acute2) were higher than after the last treatment (acute1), but still lower than at baseline (acute0).

Table 5: *Repeated Measures ANOVA for Acute AD severity. Within Subjects Effects*

	Sum of Squares	df	Mean Square	F	p	η²p
AD acute	59.23	2	29.62	12.44	<.001	0.609
AD acute * group	4.80	2	2.40	1.01	0.387	0.112

3.2.1.1 Estimated marginal means

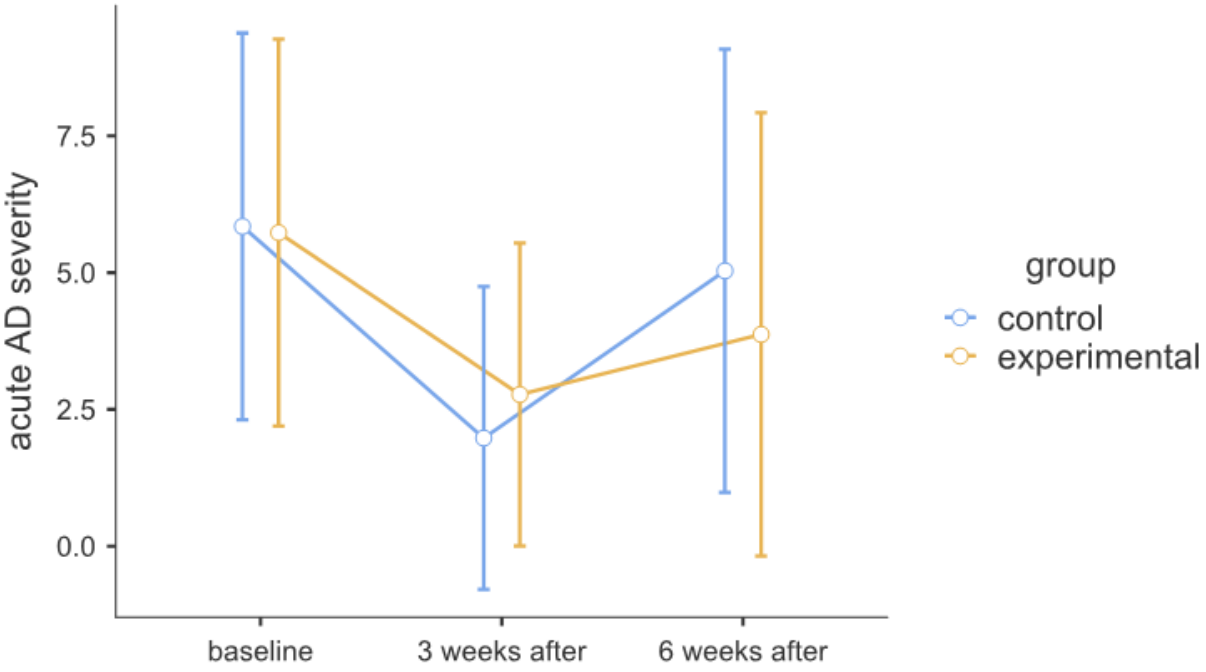

Figure 5: *Estimated Marginal Means for Acute AD severity Over Time by Group*

Table 6: *Estimated Marginal Means - AD severity acute ⁎ group*

				95% Confidence Interval	
group	**AD acute**	**Mean**	**SE**	**Lower**	**Upper**
control	baseline	5.85	1.53	2.31095	9.38
	3 weeks after	1.98	1.20	-0.79345	4.75
	6 weeks after	5.03	1.76	0.98248	9.09
experimental	baseline	5.73	1.53	2.19695	9.27
	3 weeks after	2.77	1.20	0.00255	5.54
	6 weeks after	3.87	1.76	-0.17952	7.92

A highly significant effect of the group on the acute AD severity occurred.

There was a statistically significant main effect of time (AD acute), with a p-value less than 0.001. The effect size, $\eta^2p = 0.609$, suggests a large effect, meaning that the time points (baseline, 3 weeks, and 6 weeks) significantly impact AD severity. Given the statistical significance and the large effect size, it can be concluded with confidence that AD severity changes significantly over time.

The interaction between time and group was not statistically significant ($p = 0.387$), which means that the pattern of changes in AD severity over time does not differ significantly between the control and experimental groups. However, $\eta^2p = 0.112$ suggests a small effect size, meaning there may be a slight trend toward group differences, but this is not strong enough to reach statistical significance.

3.2.2 EASI total

A mixed-design ANOVA was conducted to compare total EASI scores between the control and experimental groups over time. Total0 refers to the baseline acute EASI score, while total1 and total2 represent the second and third measurements, respectively.

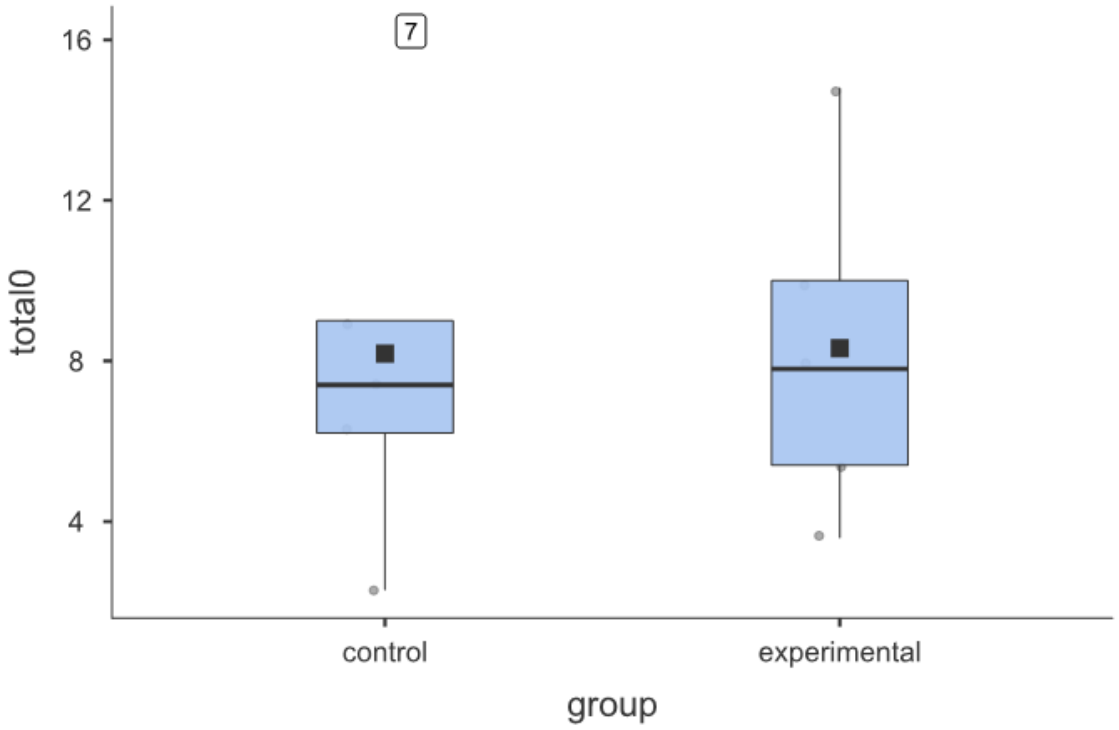

Figure 6: *Total EASI Scores at Baseline (total0)*

Both groups showed similar median total EASI scores at baseline, around 8. The horizontal line indicating the median and the black square representing the mean in the box plots were similar, which implies the data in each group were relatively evenly distributed.

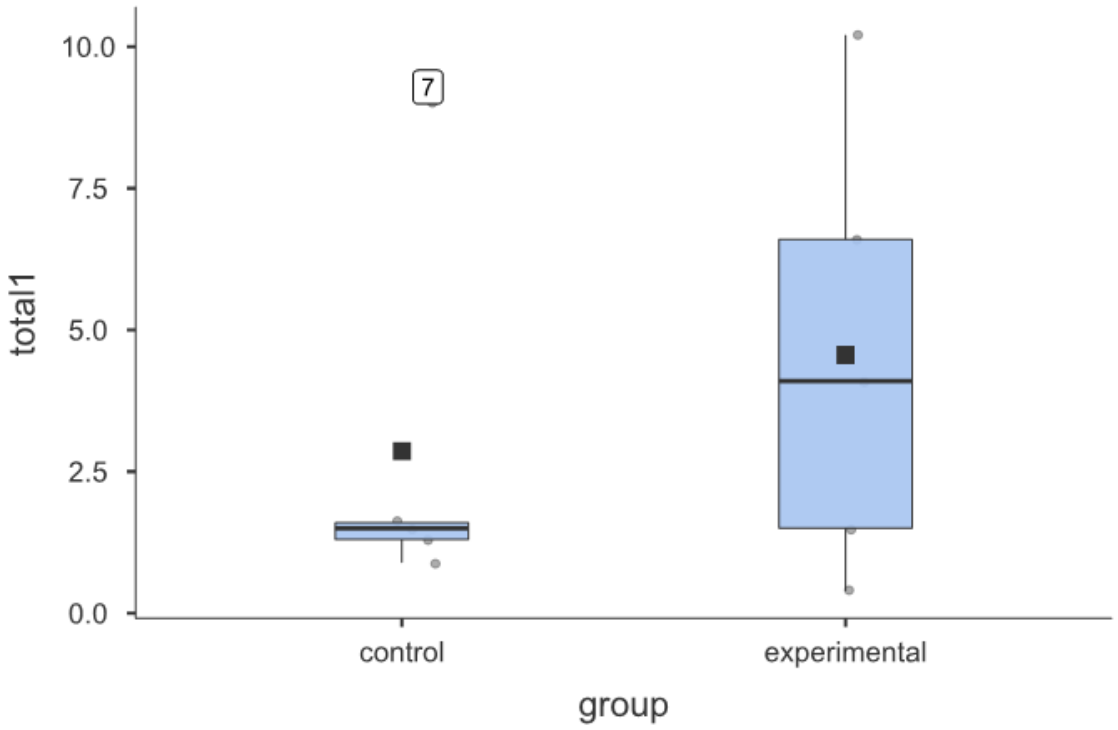

Figure 7: *Total EASI Scores after the Last Treatment (total1)*

Figure 7 displays the total EASI scores after the 3-week treatment period. The mean scores are slightly above the median, indicating light skewness. The control group showed a low median score, with a narrow interquartile range and minimal variation among participants. The experimental group demonstrated a wider range and higher scores. Compared to the baseline, both groups showed reduced EASI scores following treatment.

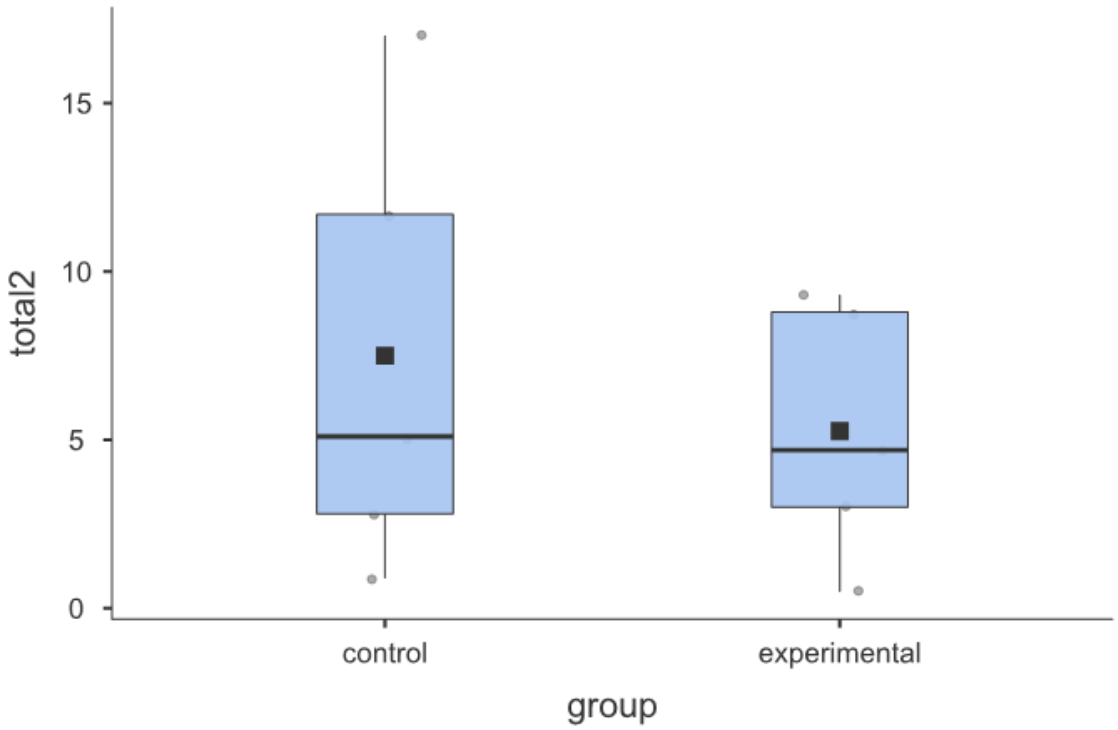

Figure 8: *Total EASI Scores at the 6-week follow-up*

Figure 8 shows the total EASI scores at the 6-week follow-up. In both groups the means were comparable, and the EASI total scores at follow-up (total2) were higher than after the last treatment (total1) but still lower than at baseline (total0).

Table 7: *Repeated Measures ANOVA for Total AD severity. Within Subjects Effects*

	Sum of Squares	df	Mean Square	F	p	η²p
AD total	104.1	2	52.06	9.66	0.002	0.547
AD total * group	19.7	2	9.84	1.83	0.193	0.186

3.2.2.1 Estimated marginal means

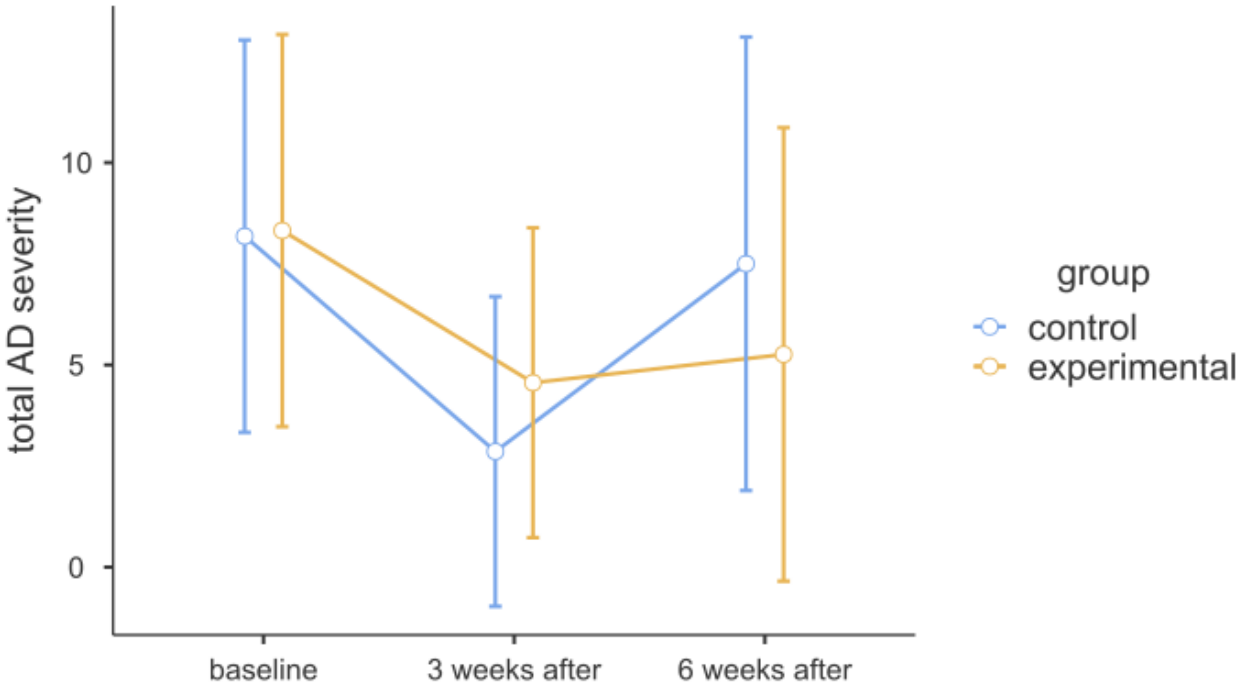

Figure 9: *Estimated Marginal Means of Total AD Severity Over Time by Group*

Table 8: *Estimated Marginal Means - AD severity total ⁎ group*

				95% Confidence Interval	
group	**AD total**	**Mean**	**SE**	**Lower**	**Upper**
control	baseline	8.18	2.10	3.332	13.03
	3 weeks after	2.86	1.66	-0.969	6.69
	6 weeks after	7.50	2.43	1.896	13.10
experimental	baseline	8.32	2.10	3.472	13.17
	3 weeks after	4.56	1.66	0.731	8.39
	6 weeks after	5.26	2.43	-0.344	10.86

A statistically significant effect of the group on the total AD severity can be observed ($F = 9.66$, $p = 0.002$, partial $\eta^2 = 0.547$), meaning that intervention groups differed considerably. There was no statistically significant interaction between time and group ($F = 1.83$, $p = 0.193$, partial $\eta^2 = 0.186$).

3.2.3 EASI chronic

A mixed-design ANOVA was conducted to compare chronic EASI scores between the control and experimental groups over time. Chronic0 refers to the baseline acute EASI score, while chronic1 and chronic2 represent the second and third measurements, respectively.

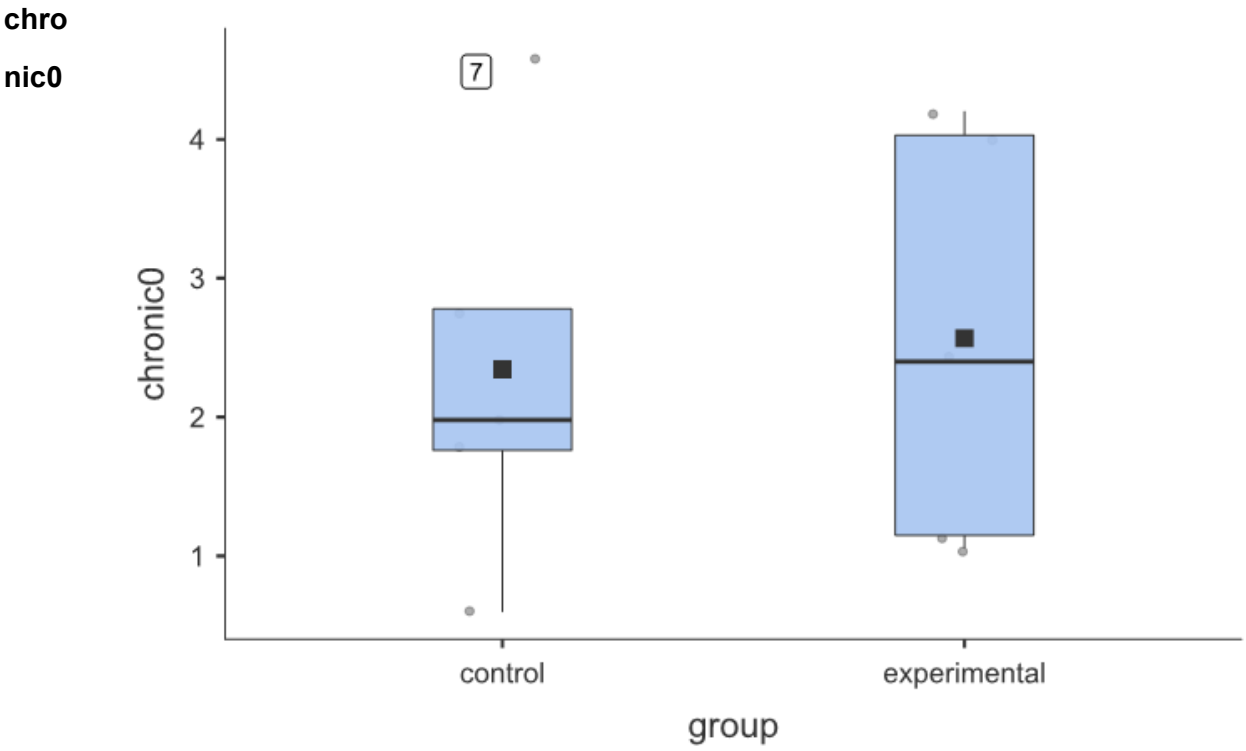

Figure 10: *Chronic EASI Scores at Baseline (chronic0)*

Both groups showed similar median chronic EASI scores at baseline, around 2. The horizontal line indicating the median and the black square representing the mean in the box plots were similar, which implies the data in each group were relatively evenly distributed.

chro

nic1

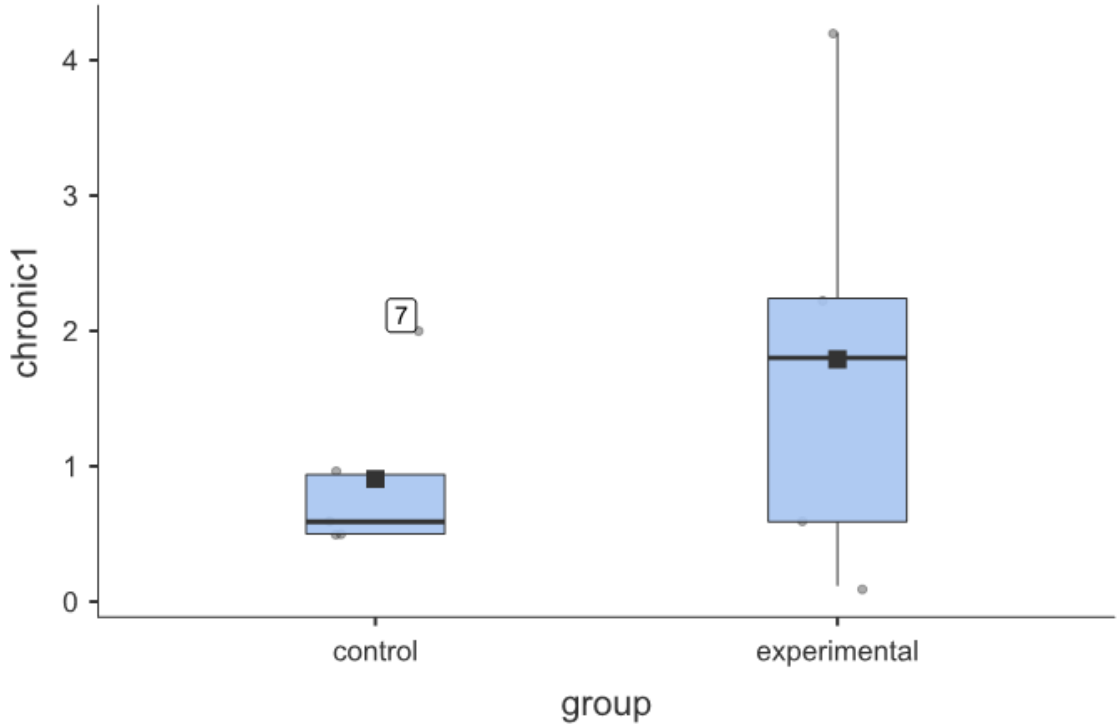

Figure 11: *Chronic EASI Scores after the Last Treatment (chronic1)*

Figure 11 displays the chronic EASI scores after the 3-week treatment period. The mean and median scores were similar within each of the groups. The control group showed a low median score, with a relatively narrow interquartile range and little variation among participants. The experimental group demonstrated a slightly narrower range compared to the baseline; both groups showed reduced EASI scores following treatment.

chro

nic2

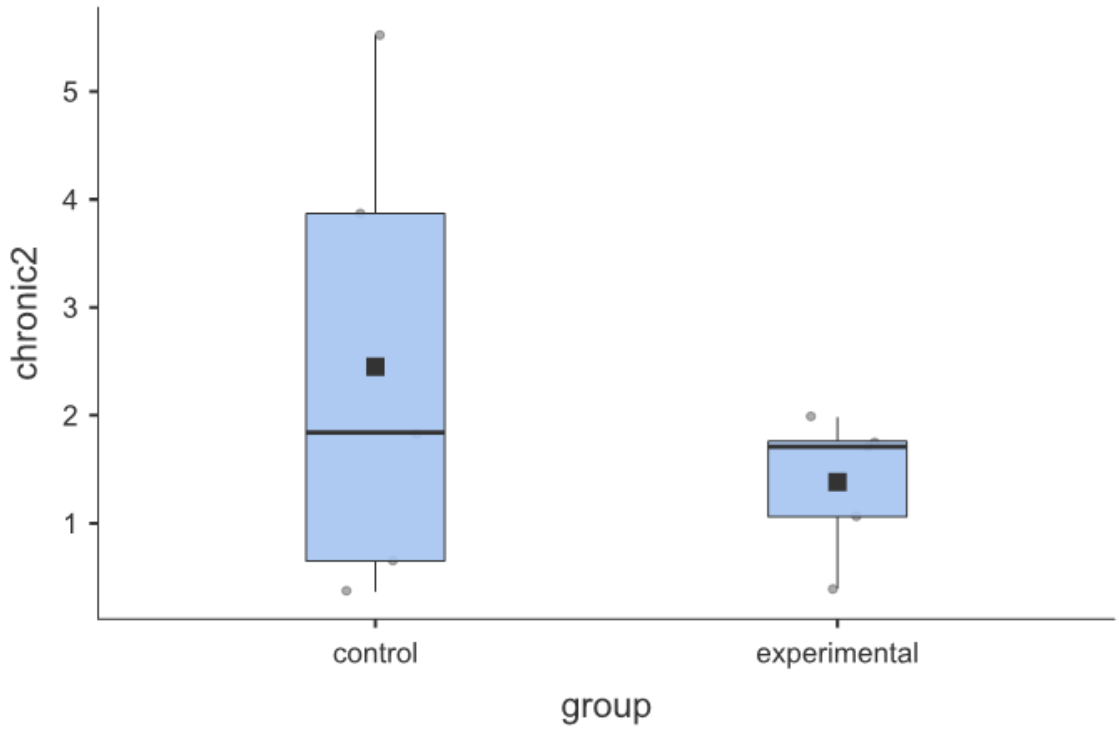

Figure 12: *Chronic EASI Scores at the 6-week follow-up*

Figure 12 shows the chronic EASI scores at the 6-week follow-up. The distribution in the control group is relative wide, the means in both groups are comparable. In both groups, the EASI chronic scores at follow-up (chronic2) were higher than after the last treatment (chronic1), but still lower than at baseline (chronic0).

Table 9: *Repeated Measures ANOVA for Chronic AD Severity. Within Subjects Effects*

	Sum of Squares	df	Mean Square	F	p	η^2p
AD chronic	6.14	2	3.070	3.52	0.054	0.306
AD chronic * group	4.93	2	2.83	2.83	0.089	0.261

3.2.3.1 Estimated marginal means

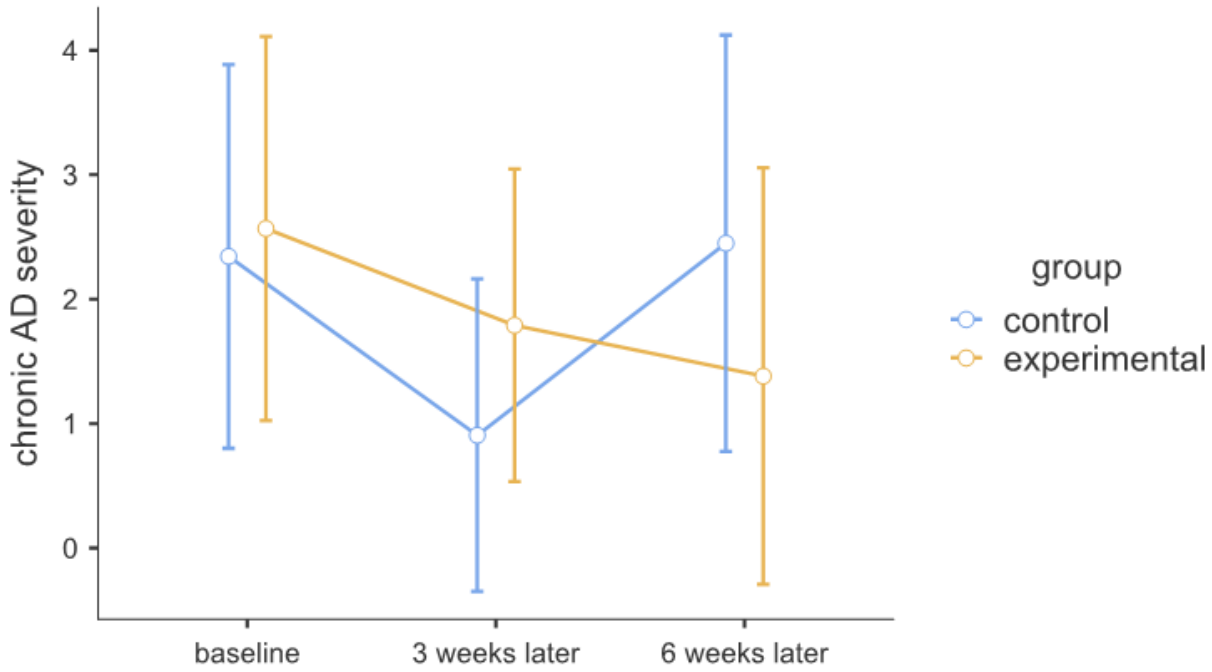

Figure 13: *Estimated Marginal Means of Chronic AD severity Over Time by Group*

Table 10: *Estimated Marginal Means - AD severity chronic ✲ group*

				95% Confidence Interval	
group	**AD chronic**	**Mean**	**SE**	**Lower**	**Upper**
control	baseline	2.34	0.67	0.801	3.89
	3 weeks after	0.91	0.55	-0.350	2.16
	6 weeks after	2.45	0.73	0.777	4.12
experimental	baseline	2.57	0.67	1.025	4.11
	3 weeks after	1.79	0.55	0.534	3.05
	6 weeks after	1.38	0.73	-0.291	3.06

A statistically insignificant effect of the group on the chronic AD severity can be observed ($F = 3.52$, $p = 0.054$, partial $\eta^2 = 0.306$), meaning that intervention groups did not differ considerably. There was an insignificant interaction between time and group ($F = 4.93$, $p = 0.089$, partial $\eta^2 = 0.261$). There was no statistically significant difference in chronic scores for the control and experimental groups.

3.3. EASI surface

The outcome measure AD surface was analysed with a non-parametric Friedmann test, as the assumption of normality was violated for all three time points in the control group. The test showed a statistically significant difference in the surface parameter across the three time points (p = 0.029). The effect size, measured by Kendall's W, was = 0.12, indicating a small effect.

Table 11: *Repeated Measures ANOVA (Non-parametric)*

χ^2	df	p	Ken W
7.06	2	0.029	0.12

Follow-up analysis with the Durbin-Conover post-hoc test revealed that the surface parameter changed significantly after the 3-week therapy (surface1) compared to baseline (surface0). No significant difference was found between post-intervention and follow-up time points (p = 0.891).

Table 12: *Pairwise Comparisons (Durbin-Conover)*

	p
surface0 - surface1	0.017
surface0 - surface2	0.012
surface1 - surface2	0.891

Descriptive statistics for surface scores across time points are presented in Table 13.

Table 13: *Changes in Surface Scores Over Time*

	Mean	Median
surface0	8.12	4.15
surface1	5.66	3.05
surface2	5.61	4.50

4 Discussion

Out of the four acquired parameter measures of the AD severity (acute, total, chronic, surface), the acute AD severity parameter is the main subject of discussion in this chapter.

A default statistical analysis seemed to be a good choice because of potential missing essential data and losing the complete picture of the EASI scoring system. Exploring all corresponding outcome measures additionally supervised the evaluation process of the received figures. The total AD severity is a sum of acute and chronic parameters, so the similarity of the acute and total AD scores was predictable. The main effect on total AD severity was significant as well and just slightly smaller, as the part of the data representing chronic AD reduces the overall outcome. Understandably, the effect on the chronic AD severity was much less; however, it still delivered a statistically insignificant effect ($p = 0.054$). As could be expected, a three-week treatment period is probably too short to observe a large change in the chronic severity score of a chronic inflammatory condition. Still, the plot showing the estimated marginal means of chronic AD outcomes seems to show that the experimental group (site 52) improved almost linearly. In no other outcome measure was the difference of the estimated marginal means so powerfully expressed.

The effect of treatment on the AD surface parameter, assessed using mixed ANOVA, was not statistically significant and could not be reliably interpreted due to the distributional issues within the control group. As a result, a non-parametric approach was applied. While the Friedman test revealed a significant overall effect, and the Durbin-Conover post hoc test suggested sustained treatment effects over time, these nonparametric tests do not permit the evaluation of interaction effects. Owing to the limited sample size and small effect size, the interpretability of these findings is restricted, with AD surface as a single parameter providing less informative value compared to composite mesures such as the analog scale. Therefore, it can only be assumed that both groups followed a similar pattern of change over time. No statistically significant difference in treatment effects between groups could be determined.

Returning to the primary focus of discussion: the results showed a significant group effect on acute AD severity ($p < 0.001$, $\eta^2p = 0.609$), with severity decreasing at 3 weeks and rising again at 6 weeks in both groups.

Table 14: *Comparison of Means – Acute AD Severity*

control group:	experimental group:
baseline: 5.85	baseline: 5.73
- 3.87	*- 2.96*
3 weeks: 1.98	3 weeks: 2.77
+ 3.05	*+ 1.1*
6 weeks: 5.03	6 weeks: 3.87

The comparison of the means above illuminates that the acute AD severity score in the control group improved faster, but then severity increased back toward baseline levels, whereas in the experimental group the improvement of the symptoms was slower, though scored better at the last measurement.

The results may be interpreted regarding the potential effectiveness of WBT and OMT in different phases of AD treatment: the acute phase (initial clearance) and maintenance therapy (long-term disease control). The goal during the acute phase of AD treatment is to quickly reduce symptoms and improve the patient's condition. The aim of maintenance therapy is to keep the disease under control over time, minimising flare-ups and maintaining lower severity (Tang et al., 2014). At 3 weeks after treatment, the control group showed a significant drop in AD severity. By 6 weeks, the severity increased back to near baseline levels. This suggests that while there was some temporary improvement, the WBC treatment might not have provided lasting relief. The first one-arm controlled trial on WBC on AD patients (Klimenko, 2008) reported lasting improvement of the severity score, pruritus, and the quality of sleep that persisted up till the last measurement, which took place 8 weeks after the 4-week therapy period. This observation led the author to hypothesise that the full therapeutic potential may not had been realised due to the insufficient duration of the treatment period. While the overall skin scores did not change significantly over time, eight participants with mild-to-moderate atopic dermatitis from another single-arm trial demonstrated sustained symptom improvement at the three-week follow-up (Kepinska-Szyszkowska, 2020). The authors implied that WBC may encourage a long process of AD care because of its anti-inflammatory and anti-pruritic

impact on the nervous system; however, the temporary relief of acute AD symptoms in the group treated with WBC may suggest that WBC does not provide lasting disease control.

OMT resulted in a moderate improvement at 3 weeks. By 6 weeks, the experimental group's severity slightly increased but remained lower than at the baseline. OMT thus appears to have a slight advantage over the control group in terms of long-term disease control, with a small reduction in severity maintained at 6 weeks, suggesting it may be better suited for maintenance therapy. Five out of six patients in a single-arm, pre-post study (Pieper, 2016) reported symptoms severity improvements in patients treated with OMT; however, the therapist evaluated these changes himself. In a three-armed, peer-reviewed RCT with 120 participants (Rotter, 2022) there was no change in EASI scores after five semi-standardised osteopathic treatments over 12 weeks and 14 weeks of follow-up. Besides, it was the first study reporting that OMT, as well as acupuncture, may halve topical corticosteroid doses despite unaltered AD severity scores. In a trial by Hosono, three individuals resistant to corticosteroids with moderate-to-severe AD experienced relief after 15 OMT sessions focused on treating muscular stiffness of the cervical spine (2020). The authors hypothesised that it was an effect of improvement of skin's autoimmune and circulatory function and restoration of the autonomic nerve balance.

The current data indicate that, unlike earlier single-arm trials that demonstrated long-term benefits with WBC, its short-term usage may only give transient alleviation from acute AD symptoms. In contrast, OMT demonstrated a more prolonged, albeit mild, effect, indicating its potential for long-term management. These distinctions highlight the significance of treatment length, implying that OMT may be better suited for maintenance therapy, whereas WBC may necessitate longer treatment to provide long-term benefits.

For condition-modifying strategies, gaining control before maintaining control with maintenance therapy may be a crucial paradigm. As observed in fourteen out of twenty randomised controlled trials (Tang et al., 2014), a higher risk of relapse was linked to the failure to control AD symptoms within initial treatment. The results of this trial allow the statement that WBC might be an effective treatment for initial clearance and OMT could effectively support long-term disease control. Both therapies could help break the vicious cycle of inflammation and barrier impairment in AD.

This is the first randomised, controlled trial investigating WBC and OMT in patients with AD. The study's strongest point was the remarkable baseline homogeneity in terms of disease severity, which increased the internal validity. Little intergroup baseline differences in age and BMI ensured a reasonably normal distribution within the relatively small sample size. Patients adhered to the trial intervention with excellent compliance. The present study has some limitations. Even if the minimum sample size for a measurable effect was achieved, future studies should include more AD patients for greater reliability. We should further investigate possible therapy effects in individuals with severe AD. One of the study's possible sources of bias was that the experimental group spent more time with the therapist; it is unclear if ten sessions (instead of three) are an adequate compensation for the physical contact. The fact that at the enrollment most participants showed more interest in WBC possibly counteracts this risk of asymmetry.

In conclusion, this study demonstrates that WBC may effectively relieve acute AD symptoms, but its benefits are short-lived without extended treatment. In contrast, OMT shows more sustained improvements, making it a promising option for long-term disease control. These findings highlight the importance of treatment duration, suggesting that WBC may be better suited for initial clearance, while OMT may offer greater benefit for maintaining disease control over time.

5 REFERENCES

Arbes Jr., S. J., Gergen, P. J., Elliott, L., & Zeldin, D. C. (2005). Prevalences of positive skin test responses to 10 common allergens in the US population: Results from the Third National Health and Nutrition Examination Survey. *Journal of Allergy and Clinical Immunology*, *116*(2), 377–383. https://doi.org/10.1016/j.jaci.2005.05.017

Barłowska-Trybulec, M., Zawojska, K., Szklarczyk, J., & Góralska, M. (2022). Effect of whole body cryotherapy on low back pain and release of endorphins and stress hormones in patients with lumbar spine osteoarthritis. *Reumatologia/Rheumatology*, *60*(4), 247–251. https://doi.org/10.5114/reum.2022.119040

Boer, M., Duchnik, E., Maleszka, R., & Marchlewicz, M. (2016). Structural and biophysical characteristics of human skin in maintaining proper epidermal barrier function. *Advances in Dermatology and Allergology*, *1*, 1–5. https://doi.org/10.5114/pdia.2015.48037

Bonamonte, D., Filoni, A., Vestita, M., Romita, P., Foti, C., & Angelini, G. (2019). The Role of the Environmental Risk Factors in the Pathogenesis and Clinical Outcome of Atopic Dermatitis. *BioMed Research International*, *2019*, 1–11. https://doi.org/10.1155/2019/2450605

Bouzigon, R., Grappe, F., Ravier, G., & Dugue, B. (2016). Whole- and partial-body cryostimulation/cryotherapy: Current technologies and practical applications. *Journal of Thermal Biology*, *61*, 67–81. https://doi.org/10.1016/j.jtherbio.2016.08.009

Bożek, A., & Reich, A. (2017). Assessment of Intra- and Inter-Rater Reliability of Three Methods for Measuring Atopic Dermatitis Severity: EASI, Objective SCORAD, and IGA. *Dermatology*, *233*(1), 16–22. https://doi.org/10.1159/000472711

Cahana, A. & Hurst, S. A. (2008). *Voluntary Informed Consent in Research and Clinical Care: An Update.Pain Pract.*, 8(6):446-51.

Campbell, S. M., Sammons, D. L., Sarsama-Nixon, R. M., Holsinger, J. M., Stephenson, S., & Walkowski, S. (2011). Dermatology: A Specialty That Exemplifies the Osteopathic Medical Profession. *JAOA*, *Vol 111*, 335–338.

Chopra, R., Vakharia, P. P., Simpson, E. L., Paller, A. S., & Silverberg, J. I. (2017). Severity assessments used for inclusion criteria and baseline severity evaluation in atopic dermatitis clinical trials: A systematic review. *Journal of the European Academy of Dermatology and Venereology*, *31*(11), 1890–1899. https://doi.org/10.1111/jdv.14483

Dery, M.A. , Yonuschot G, Winterson B.J. (2000). The effects of manually applied intermittent pulsation pressure to rat ventral thorax on lymph transport. *Lymphology*. 33(2):58-61.

Doets, J. J. R., Topper, M., & Nugter, A. M. (2021). A systematic review and meta-analysis of the effect of whole body cryotherapy on mental health problems. *Complementary Therapies in Medicine*, *63*, 102783. https://doi.org/10.1016/j.ctim.2021.102783

Douzi, W., Dupuy, O., Tanneau, M., Boucard, G., Bouzigon, R., & Dugué, B. (2019). 3-min whole body cryotherapy/cryostimulation after training in the evening improves sleep quality in physically active men. *European Journal of Sport Science*, *19*(6), 860–867. https://doi.org/10.1080/17461391.2018.1551937

Drucker, A. M., Wang, A. R., Li, W.-Q., Sevetson, E., Block, J. K., & Qureshi, A. A. (2017). The Burden of Atopic Dermatitis: Summary of a Report for the National Eczema Association. *Journal of Investigative Dermatology*, *137*(1), 26–30. https://doi.org/10.1016/j.jid.2016.07.012

Eckert, L. (2018). The burden of atopic dermatitis in US adults: Health care resource utilization data from the 2013 National Health and Wellness Survey. *J AM ACAD DERMATOL*, *78*(1).

Eichenfield, L. F., Tom, W. L., Berger, T. G., Krol, A., Paller, A. S., Schwarzenberger, K., Bergman, J. N., Chamlin, S. L., Cohen, D. E., Cooper, K. D., Cordoro, K. M., Davis, D. M., Feldman, S. R., Hanifin, J. M., Margolis, D. J., Silverman, R. A., Simpson, E. L., Williams, H. C., Elmets, C. A., … Sidbury, R. (2014). Guidelines of care for the management of atopic dermatitis. *Journal of the American Academy of Dermatology*, *71*(1), 116–132. https://doi.org/10.1016/j.jaad.2014.03.023

Giesey, R., Kamel, J., Delost, G., & Lloyd, J. (2020). DERMS DO 5: A Proposed Curriculum for Dermatologic Training in 5 Osteopathic Competencies. *Journal of Osteopathic Medicine*, *120*(11), 740–748. https://doi.org/10.7556/jaoa.2020.118

Glass, G., Peckham P.D., Sanders J.R. (1972). *Consequences of Failure to meet Assumptions Underlying the Fixed Effects Analyses of Variance and Covariance. Review of Educational Research*.

Gunga H.C. & Steinach M. (2016). Wärmehaushalt und Temperaturregulation. In Speckmann, E.-J., Hescheler, J., & Köhling, R. (2013). *Physiologie*., 625 - 646

Han, H., Roan, F., & Ziegler, S. F. (2018). *The atopic march: Current insights into skin barrier dysfunction and epithelial cell-derived cytokines*.

Hanifin, J. M., Baghoomian, W., Grinich, E., Leshem, Y. A., Jacobson, M., & Simpson, E. L. (2022). The Eczema Area and Severity Index—A Practical Guide. *Dermatitis*, *33*(3), 187–192. https://doi.org/10.1097/DER.0000000000000895

Hanifin, J. M. & Rajka G. (1980). *Diagnostic Features of Atopic Dermatitis*. *Acta Dermato-Venerologica,* 60(92), 44-47

Hausswirth, C., Schaal, K., Le Meur, Y., Bieuzen, F., Filliard, J.-R., Volondat, M., & Louis, J. (2013). Parasympathetic Activity and Blood Catecholamine Responses Following a Single Partial-Body Cryostimulation and a Whole-Body Cryostimulation. *PLoS ONE*, *8*(8), e72658. https://doi.org/10.1371/journal.pone.0072658

Hesselmar, B., Hicke-Roberts, A., & Wennergren, G. (2015). *Allergy in Children in Hand Versus Machine Dishwashing*. *135*(3).

Hesselmar, B., Sjöberg, F., Saalman, R., Åberg, N., Adlerberth, I., & Wold, A. E. (2013). Pacifier Cleaning Practices and Risk of Allergy Development. *Pediatrics*, *131*(6), e1829–e1837. https://doi.org/10.1542/peds.2012-3345

Hibler, J., Perkins, J., Eland, D., & Sammons, D. (2014). Osteopathic Manipulative Medicine for Inflammatory Skin Diseases. *Journal Of The American Osteopathic College Of Dermatology*, *31*, 11–13.

Hodge, L. M., & Downey, H. F. (2011). Lymphatic pump treatment enhances the lymphatic and immune systems. *Experimental Biology and Medicine*, *236*(10), 1109–1115. https://doi.org/10.1258/ebm.2011.011057

Holm, E. A., & Jemec, G. B. E. (2004). Time Spent on Treatment of Atopic Dermatitis: A New Method of Measuring Pediatric Morbidity? *Pediatric Dermatology*, *21*(6), 623–627. https://doi.org/10.1111/j.0736-8046.2004.21601.x

Hosono, S., Fujita, K., Nimura, A., & Akita, K. (2020). Release of cervical muscular tension improved severe pruritus in moderate-to-severe atopic dermatitis: A case series. *JAAD Case Reports*, *6*(6), 510–513. https://doi.org/10.1016/j.jdcr.2020.03.018

Housman, T. S., Patel, M. J., Camacho, F., Feldman, S. R., Fleischer, A. B., & Balkrishnan, R. (2002). Use of the Self-Administered Eczema Area and Severity Index by parent caregivers: Results of a validation study. *British Journal of Dermatology*, *147*(6), 1192–1198. https://doi.org/10.1046/j.1365-2133.2002.05031.x

Hruby, R. J., & Martinez, E. S. (2021). The Lymphatic System: An Osteopathic Review. *Cureus*. https://doi.org/10.7759/cureus.16448

Kang J.-H. (2013). The comparison of the effect of thermotherapy and cryotherapy on the skin., *Asian J. Beauty Cosmetol.* 11:281-288

Kasraie, S., Niebuhr, M., & Werfel, T. (2010). *Interleukin (IL)31 induces proinflammatory cytokines in human monocytes and macrophages following stimulation with staphylococcal exotoxins*.

Kelly, E. A., Forootan, N. S., Checketts, J. X., Frank, A., & Tangen, C. L. (2023). Retrospective analysis of whole-body cryotherapy adverse effects in Division I collegiate athletes. *Journal of Osteopathic Medicine*, *123*(5), 249–257. https://doi.org/10.1515/jom-2022-0156

Kepinska-Szyszkowska, M., Misiorek, A., Kapinska-Mrowiecka, M., Tabak, J., & Malina, K. (2020). Assessment of the Influence Systemic Cryotherapy Exerts on Chosen Skin Scores of Patients with Atopic Dermatitis: Pilot Study. *BioMed Research International*, *2020*, 1–7. https://doi.org/10.1155/2020/5279642

Kissling, S., & Wüthrich, B. (1993). Verlauf der atopischen Dermatitis nach dem Kleinkindesalter. *Hautarzt*, *44*, 569–573.

Klimenko, T., Ahvenainen, S., & Karvonen, S.-L. (2008). Whole-Body Cryotherapy in Atopic Dermatitis. *Archives of Dermatology*, *144*(6). https://doi.org/10.1001/archderm.144.6.806

Knott, E.M., Tune J.D., Stoll S.T., Downey H.F. (2005). Increased lymphatic flow in the thoracic duct during manipulative intervention. J Am Osteopath Assoc. 105(10):447-56.

Koutroulis, I., Petrova, K., Kratimenos, P., & Gaughan, J. (2014). Frequency of bathing in the management of atopic dermatitis: To bathe or not to bathe? *Clinical Pediatrics*, *53*(7), 677–681. https://doi.org/10.1177/0009922814526980

Lal, K., Lowe, E., Treyger, G., & Li, T. S. (2016). Combining Treatment Modalities for Atopic Dermatitis. *Practical Dermatology*, *9*, 26–32.

Lambers, H., Piessens, S., Bloem, A., Pronk, H., & Finkel, P. (2006). Natural skin surface pH is on average below 5, which is beneficial for its resident flora. *International Journal of Cosmetic Science*, *28*(5), 359–370. https://doi.org/10.1111/j.1467-2494.2006.00344.x

Langan, S. M., Irvine, A. D., & Weidinger, S. (2020). Atopic dermatitis. *The Lancet*, *396*(10247), 345–360. https://doi.org/10.1016/S0140-6736(20)31286-1

Leone, A. R., Rowane, M. P., & Lloyd, J. R. (2018). *Pediatric Atopic Dermatitis: Utilizing OMT as an Adjunct Treatment*.

Lewis-Jones, S. (2006). Quality of life and childhood atopic dermatitis: The misery of living with childhood eczema. *QUALITY OF LIFE*.

Lobefaro, F., Gualdi, G., Di Nuzzo, S., & Amerio, P. (2022). Atopic Dermatitis: Clinical Aspects and Unmet Needs. *Biomedicines*, *10*(11), 2927. https://doi.org/10.3390/biomedicines10112927

Lubkowska, A. (2012). Cryotherapy: Physiological Considerations and Applications to Physical Therapy. *InTech.*

Maarouf, M., Hendricks, A. J., & Shi, V. Y. (2019). Bathing additives for atopic dermatitis – A systematic review. *Dermatitis*, *30*(3), 191–197. https://doi.org/10.1097/DER.0000000000000459

McKenzie, C., & Silverberg, J. I. (2019). The prevalence and persistence of atopic dermatitis in urban United States children. *Annals of Allergy, Asthma & Immunology*, *123*(2), 173-178.e1. https://doi.org/10.1016/j.anai.2019.05.014

Metsämuuronen, J. (2024). *Common language interpretation of r effect, Cohen's d, and Cohen's f*.

Miller, E., Markiewicz, Ł., Saluk, J., & Majsterek, I. (2012). Effect of short-term cryostimulation on antioxidative status and its clinical applications in humans. *European Journal of Applied Physiology*, *112*(5), 1645–1652. https://doi.org/10.1007/s00421-011-2122-x

Miller, E., Mrowicka, M., Malinowska, K., Mrowicki, J., Saluk-Juszczak, J., & Kędziora, J. (2011). Effects of whole-body cryotherapy on a total antioxidative status and activities of antioxidative enzymes in blood of depressive multiple sclerosis patients. *The World Journal of Biological Psychiatry*, *12*(3), 223–227. https://doi.org/10.3109/15622975.2010.518626

Misiorek, A., & Szyszkowska-Kępińska, M. (2021). Evaluation of the influence of whole-body cryotherapy on selected skin parameters in healthy individuals: Pilot study. *Cryobiology*, *100*, 77–80. https://doi.org/10.1016/j.cryobiol.2021.03.007

Missmann, M., Himsl, M., Mur, E., Ulmer, H., & Marschang, P. (2016). Impact of Whole Body Cryotherapy at −110 °C on Subjects with Arterial Hypertension. *Archivum Immunologiae et Therapiae Experimentalis*, *64*(1), 75–82. https://doi.org/10.1007/s00005-015-0363-9

Zhang, H., Mohan, G. C., Bao, L., Many, B., & Chan, L. S. (2017). Diacerein inhibits the pro-atherogenic & pro-inflammatory effects of IL-1 on human keratinocytes & endothelial cells. *PloS One*, *12*(3), e0173981. https://doi.org/10.1371/journal.pone.0173981

Moustgaard, H., Clayton, G. L., Jones, H. E., Boutron, I., Jørgensen, L., Laursen, D. R. T., Olsen, M. F., Paludan-Müller, A., Ravaud, P., Savović, J., Sterne, J. A. C., Higgins, J. P. T., & Hróbjartsson, A. (2020). Impact of blinding on estimated treatment effects in randomised clinical trials: Meta-epidemiological study. *The BMJ*, *368*, l6802. https://doi.org/10.1136/bmj.l6802

Nakashima, C., Yanagihara, S., & Otsuka, A. (2022). Innovation in the treatment of atopic dermatitis: Emerging topical and oral Janus kinase inhibitors. *Allergology International*, *71*(1), 40–46. https://doi.org/10.1016/j.alit.2021.10.004

Nakatsuji, T., & Gallo, R. L. (2019). The role of the skin microbiome in atopic dermatitis. *Annals of Allergy, Asthma & Immunology*, *122*(3), 263–269. https://doi.org/10.1016/j.anai.2018.12.003

National Eczema Association. (n.d.). *Eczema Treatments in Development*. https://nationaleczema.org/research/eczema-treatment-research/

Paddon-Jones D.J., Quigley B.M. (1997). Effect of cryotherapy on muscle soreness and strength following eccentric exercise. *Int J Sports Med.*, 18(8):588-93

Panacek, E. A., & Thompson, C. B. (2007). Sampling methods: Selecting your subjects. *Air Medical Journal*, *26*(2), 75–78. https://doi.org/10.1016/j.amj.2007.01.001

Park, K. Y., Park, M. K., Seok, J., Li, K., & Seo, S. J. (2016). Clinical characteristics of Korean patients with filaggrin-related atopic dermatitis. *Clinical and Experimental Dermatology*, *41*(6), 595–600. https://doi.org/10.1111/ced.12854

Parravicini, G., & Bergna, A. (2017). Biological effects of direct and indirect manipulation of the fascial system. Narrative review. *Journal of Bodywork and Movement Therapies*, *21*(2), 435–445. https://doi.org/10.1016/j.jbmt.2017.01.005

Patel, K. R., Immaneni, S., Singam, V., Rastogi, S., & Silverberg, J. I. (2019). Association between atopic dermatitis, depression, and suicidal ideation: A systematic review and meta-analysis. *Journal of the American Academy of Dermatology*, *80*(2), 402–410. https://doi.org/10.1016/j.jaad.2018.08.063

Pieper M. (2016), Osteopathy in atopic dermatitis in adults. A pilot study. *Thesis fo Bachelor of Science, Dresden International University*

Piotrowska, A., Aszklar, K., Dzidek, A., Ptaszek, B., Czerwińska-Ledwig, O., & Pilch, W. (2021). The impact of a single whole body cryostimulation treatment on selected skin properties of healthy young subjects. *Cryobiology*, *100*, 96–100. https://doi.org/10.1016/j.cryobiol.2021.03.003

Polidori, G., Taiar, R., Legrand, F., Beaumont, F., Murer, S., Bogard, F., & Boyer, F. C. (2018). Infrared thermography for assessing skin temperature differences between Partial Body Cryotherapy and Whole Body Cryotherapy devices at −140 °C. *Infrared Physics & Technology*, *93*, 158–161. https://doi.org/10.1016/j.infrared.2018.07.025

Ring, J. (2016). *Atopic Dermatitis. Eczema*. Springer International Publishing, 9-25.

Rodríguez, E., Baurecht, H., Herberich, E., Wagenpfeil, S., Brown, S. J., Cordell, H. J., Irvine, A. D., & Weidinger, S. (2009). Meta-analysis of filaggrin polymorphisms in eczema and asthma: Robust risk factors in atopic disease. *Journal of Allergy and Clinical Immunology*, *123*(6), 1361-1370.e7. https://doi.org/10.1016/j.jaci.2009.03.036

Rotter, G., Ahnert, M. W., Geue, A. V., Icke, K., Binting, S., Tissen-Diabaté, T., Roll, S., Ortiz, M., Reinhold, T., Kass, B., Staab, D., Pfab, F., Willich, S. N., & Brinkhaus, B. (2022). Acupuncture and osteopathic medicine for atopic dermatitis: A three-armed, randomized controlled explorative clinical trial. *Clinical and Experimental Dermatology*, *47*(12), 2166–2175. https://doi.org/10.1111/ced.15340

Sadura-Sieklucka, T., Sołtysiuk, B., Karlicka, A., Sokołowska, B., Kontny, E., & Księżopolska-Orłowska, K. (2019). Effects of whole body cryotherapy in patients with rheumatoid arthritis considering immune parameters. *Reumatologia/Rheumatology*, *57*(6), 320–325. https://doi.org/10.5114/reum.2019.90825

Saloga, J. & Knop, J. (2006). Atopisches Ekzem. In Saloga, J., Angerer, P., Klimek, L., Buhl, R., Mann, W., & Knop, J. (2006). *Allergologie-Handbuch: Grundlagen und klinische Praxis, 354-364*

Saltykova, M. M., Kuzmin, I. V., & Zhuravleva, O. A. (2017). Effect of Short-term Cooling at –70°C in an Air Cryogenic Sauna on Body Temperature and Lipid Profile of Healthy People. *Human Physiology*, *43*(7), 829–833. https://doi.org/10.1134/S0362119717070180

Santer, M., Ridd, M. J., Francis, N. A., Stuart, B., Rumsby, K., Chorozoglou, M., et al. (2018). Emollient bath additives for the treatment of childhood eczema (BATHE): Multicentre pragmatic parallel group randomised controlled trial of clinical and cost effectiveness. *BMJ*, *361*, k1332. https://doi.org/10.1136/bmj.k1332

Schander, A., Downey, H.F., Hodge L.M. (2012). Lymphatic pump manipulation moblizes inflammatory mediators into lymphatic circulation. *Exp Biol Med (Maywood)*, 237(1):58-63

Schneider , W.,(2013). Anatomie der Haut. In Speckmann, E.-J., Hescheler, J., & Köhling, R. (2013). *Physiologie*, 653-656

Schwartz, D. M., Kanno, Y., Villarino, A., Ward, M., Gadina, M., & O'Shea, J. J. (2017). JAK inhibition as a therapeutic strategy for immune and inflammatory diseases. *Nature Reviews Drug Discovery*, *16*(12), 843–862. https://doi.org/10.1038/nrd.2017.201

Sherwood, L. (2010). Body Defenses. In *Human Physiology: From Cells To Systems. 7th Edition*. Cengage Learning Services, 407-450

Sidbury, R., Davis, D. M., Cohen, D. E., Cordoro, K. M., Berger, T. G., Bergman, J. N., Chamlin, S. L., Cooper, K. D., Feldman, S. R., Hanifin, J. M., Krol, A., Margolis, D. J., Paller, A. S., Schwarzenberger, K., Silverman, R. A., Simpson, E. L., Tom, W. L., Williams, H. C., Elmets, C. A., … Eichenfield, L. F. (2014). Guidelines of care for the management of atopic dermatitis. *Journal of the American Academy of Dermatology*, *71*(2), 327–349. https://doi.org/10.1016/j.jaad.2014.03.030

Simpson, E. L., Basco, M., & Hanifin, J. (2003). A cross-sectional survey of complementary and alternative medicine use in patients with atopic dermatitis. *American Journal of Contact Dermatitis: Official Journal of the American Contact Dermatitis Society*, *14*(3), 144–147. https://doi.org/10.2310/6620.2003.6156

Skrzek, A., Ciszek, A., Nowicka, D., & Dębiec-Bąk, A. (2019). Evaluation of changes in selected skin parameters under the influence of extremely low temperature. *Cryobiology*, *86*, 19–24. https://doi.org/10.1016/j.cryobiol.2019.01.005

Stanek, A., Cholewka, A., Wielkoszyński, T., Romuk, E., & Sieroń, A. (2018). Decreased Oxidative Stress in Male Patients with Active Phase Ankylosing Spondylitis Who Underwent Whole-Body Cryotherapy in Closed Cryochamber. *Oxidative Medicine and Cellular Longevity*, *2018*, 1–9. https://doi.org/10.1155/2018/7365490

Stanek, A., Wielkoszyński, T., Bartuś, S., & Cholewka, A. (2020). Whole-Body Cryostimulation Improves Inflammatory Endothelium Parameters and Decreases Oxidative

Stress in Healthy Subjects. *Antioxidants*, *9*(12), 1308. https://doi.org/10.3390/antiox9121308

Stefanovic, N., Flohr, C., & Irvine, A. D. (2020). The exposome in atopic dermatitis. *Allergy*, *75*(1), 63–74. https://doi.org/10.1111/all.13946

Tang, T. S., Bieber, T., & Williams, H. C. (2014). Are the concepts of induction of remission and treatment of subclinical inflammation in atopic dermatitis clinically useful? *Journal of Allergy and Clinical Immunology*, *133*(6), 1615-1625.e1. https://doi.org/10.1016/j.jaci.2013.12.1079

Tsoi, L. C., Rodriguez, E., Degenhardt, F., Baurecht, H., Wehkamp, U., Volks, N., Szymczak, S., Swindell, W. R., Sarkar, M. K., Raja, K., Shao, S., Patrick, M., Gao, Y., Uppala, R., Perez White, B. E., Getsios, S., Harms, P. W., Maverakis, E., Elder, J. T., … Weidinger, S. (2019). Atopic Dermatitis Is an IL-13–Dominant Disease with Greater Molecular Heterogeneity Compared to Psoriasis. *Journal of Investigative Dermatology*, *139*(7), 1480–1489. https://doi.org/10.1016/j.jid.2018.12.018

Varallo, G., Piterà, P., Fontana, J. M., Gobbi, M., Arreghini, M., Giusti, E. M., Franceschini, C., Plazzi, G., Castelnuovo, G., & Capodaglio, P. (2022). Is Whole-Body Cryostimulation an Effective Add-On Treatment in Individuals with Fibromyalgia and Obesity? A Randomized Controlled Clinical Trial. *Journal of Clinical Medicine*, *11*(15), 4324. https://doi.org/10.3390/jcm11154324

Ventura, N., & Soti, V. (2024). Integrating Osteopathic Principles for Enhanced Dermatological Outcomes: A Literature Review. *Cureus*. https://doi.org/10.7759/cureus.52665

Verzella, M., Affede, E., Di Pietrantonio, L., Cozzolino, V., & Cicchitti, L. (2022). Tissutal and Fluidic Aspects in Osteopathic Manual Therapy: A Narrative Review. *Healthcare*, *10*(6), 1014. https://doi.org/10.3390/healthcare10061014

Wilcock, I. M., Cronin, J. B., & Hing, W. A. (2006). Water Immersion: Does It Enhance Recovery From Exercise? *International Journal of Sports Physiology and Performance*, *1*(3), 195–206. https://doi.org/10.1123/ijspp.1.3.195

Wollenberg, A., Blauvelt, A., Guttman-Yassky, E., Worm, M., Lynde, C., Lacour, J. -P., Spelman, L., Katoh, N., Saeki, H., Poulin, Y., Lesiak, A., Kircik, L., Cho, S. H., Herranz, P., Cork, M. J., Peris, K., Steffensen, L. A., Bang, B., Kuznetsova, A., … the ECZTRA 1 and ECZTRA 2 study investigators. (2021). Tralokinumab for moderate-to-severe atopic dermatitis: Results from two 52-week, randomized, double-blind, multicentre, placebo-controlled phase III trials (ECZTRA 1 and ECZTRA 2)*. *British Journal of Dermatology*, *184*(3), 437–449. https://doi.org/10.1111/bjd.19574

Wollenberg, A., Kinberger, M., Arents, B., Aszodi, N., Avila Valle, G., Barbarot, S., Bieber, T., Brough, H. A., Calzavara Pinton, P., Christen-Zäch, S., Deleuran, M., Dittmann, M., Dressler, C., Fink-Wagner, A. H., Fosse, N., Gáspár, K., Gerbens, L., Gieler, U., Girolomoni, G., … Flohr, C. (2022). European guideline (EuroGuiDerm) on atopic eczema - part II: Non-systemic treatments and treatment recommendations for special AE patient populations. *Journal of the European Academy of Dermatology and Venereology : JEADV*, *36*(11), Article 11.

Yosipovitch, G., Tran, B., Papoiu, A., Russoniello, C., Wang, H., Patel, T., & Chan, Y. (2010). Effect of Itch, Scratching and Mental Stress on Autonomic Nervous System Function in Atopic Dermatitis. *Acta Dermato Venereologica*, *90*(4), 354–361. https://doi.org/10.2340/00015555-0890

Zhong, L., Wang Q., Li M., Hao P. (2021). Efficacy and Safety of Liquid Nitrogen Cryotherapy for Lichen Simplex Chronicus: A Meta-Analysis. *Dermatology.* 238(3):454-463

6 TABLES

Number Page

7 FIGURES

Number Page

8 ABBREVIATIONS

Abbreviation	Meaning
AD	Atopic Dermatitis
AOCD	American College of Dermatology
ANOVA	Analysis of Variance
BMI	Body Mass Index
BSA	Body Surface Area
CV4	Compression of the Fourth Ventricle
C0/C1	Atlanto-occipital Joint
C7/Th1	Cervicothoracic Junction
DALYs	Disability-Adjusted Life Years
EASI	Eczema Area and Severity Index
GOT	General Osteopathic Treatment
IGA	Investigator's Global Assessment
IgE	Immunoglobulin E
IL-4	Interleukin 4
IL-13	Interleukin 13
IL-33	Interleukin 33
JAK	Janus Kinase
OMT	Osteopathic Manipulative Treatment
PUVA	Psoralen plus ultraviolet A radiation
SA-EASI	Self-Administered Eczema Area and Severity Index
SALT	Skin-Associated Lymphoid Tissue
S. aureus	Staphylococcus aureus
SCORAD	Scoring Atopic Dermatitis
Th2	T helper type 2 cell
Th10–L1	From Thoracic Vertebra 10 to Lumbar Vertebra 1
Th12/L1	Thoracolumbar Junction
TSLP	Thymic Stromal Lymphopoietin
UVA1	Ultraviolet A1 radiation
UVB	Ultraviolet B radiation
VAS	Visual Analog Scale
WBC	Whole-Body Cryotherapy

Liebe_r Studienteilnehmer_in,

Danke für Ihr Interesse an der Studienteilnahme. Es ist mir wichtig, dass Sie eine informierte Entscheidung treffen. Bitte lesen Sie das Blatt sorgfältig durch.

ZUR FORSCHUNG

Diese klinische Studie wird von Monika Lammeraner in der Praxis für Physiotherapie in Kremstalstraße 53 in Krems, im Rahmen der Masterarbeit (Master of Science der Wiener Schule für Osteopathie und der Donau-Universität Krems), durchgeführt. Es werden insgesamt 28 Personen daran teilnehmen. Von der Forschung sollen Neurodermitis-Betroffene profitieren – Ziel ist es festzustellen, wie eine osteopathische Behandlung und die Kältetherapie in der Kryosauna den Schweregrad der Neurodermitis beeinflussen.

Ihre Teilnahme beginnt heute und wird voraussichtlich neun Wochen dauern. Sie werden heute neben dieser Aufklärung noch ein Formular zum Ausfüllen bekommen und werden gebeten, den Schwergrad der Neurodermitis mittels SA-EASI Score am Tablet zu beurteilen. Anschließend erfolgt Ihre erste Behandlung. Der Münzwurf entscheidet, welche Therapieform Sie in den kommenden drei Wochen bekommen: entweder sind es drei osteopathische Behandlungen oder zehn Kältebehandlungen in der Kryosauna. Beim letzten Termin werden Sie erneut gefragt, um den Schweregrad der Neurodermitis zu beurteilen. Um auch den langfristigen Effekt einschätzen zu können, wird es ebenfalls sechs Wochen nach dem letzten Termin erforderlich sein, auf die gleiche Art und Weise die Hautläsionen zu bewerten. Es ist kein persönlicher Termin notwendig; Sie bekommen den Link und werden gebeten, das Ergebnis als PDF per E-Mail zu schicken.

Um die Risiken für Sie zu minimieren, werden nur Personen zur Studie zugelassen, die die Einschlusskriterien erfüllen (im zweiten Formular sehen Sie die Ausschlusskriterien). Sollten Sie die Kältebehandlungen absolvieren, achten Sie bitte darauf, dass Ihre Haut vor dem Reingehen in die Kältekammer trocken ist (bitte auch keine frisch aufgetragene Creme). Bitte kommen Sie zu den Terminen nur im guten Allgemeinzustand. Es ist möglich, dass Sie durch Ihre Teilnahme keinen direkten Nutzen für Ihre Gesundheit ziehen. In mehreren Studien wurde bereits nachgewiesen, dass Osteopathie und Kryotherapie den Juckreiz, die Schlaf- und Lebensqualität verbessern können. Sollten im Verlauf der Studie irgendwelche Symptome, Begleiterscheinungen oder Verletzungen auftreten, teilen Sie dies bitte mit.

Jedem Teilnehmer werden beim ersten Termin 60 Euro verrechnet, um die Forschungsausgaben für das Kühlmittel (Flüssigstickstoff) zu mindern. Mit diesem kleinen Beitrag (entspricht ca. der 20% des regulären Preises), wird von mir auch erhofft, dass die Teilnehmer die Behandlungen wertschätzen und die Termine einhalten, was von entscheidender Bedeutung für den Erfolg dieser klinischen Studie ist.

Ihre Studienteilnahme ist freiwillig und unabhängig. Das Einverständnis kann jederzeit ohne Konsequenzen zurückgezogen werden.

EINWILLIGUNGSERKLÄRUNG

Name ……

Geb.Datum ……

Ich wurde ausführlich aufgeklärt und erkläre mich bereit, freiwillig **an der Studie teilzunehmen.**

Datum…… Unterschrift……

DATENSCHUTZERKLÄRUNG

Die Verarbeitung Ihrer personenbezogenen Daten in der Forschung (Name, E-Mail, Telefonnummer, Geburtsdatum, Geschlecht, Körpergröße und andere medizinische Daten) erfolgt nach den strengen Anforderungen der DSGVO. Es ist mir eine Verpflichtung, Ihre Anonymität und Privatsphäre zu schützen. Eine Weitergabe der Daten erfolgt nur in anonymisierter Form. Die Dauer der Speicherung Ihrer personenbezogenen Daten über das Ende oder den Abbruch der klinischen Studie hinaus ist durch Rechtsvorschriften geregelt.

Hiermit stimme ich **der Verarbeitung der personenbezogenen Daten** zu:

Datum…… Unterschrift……

FORMULAR

- Ich bin volljährig und noch keine 70 Jahre alt
- Atopische dermatitis wurde bei mir diagnostiziert
- Ich hatte Symptome in den letzten 12 Monaten

- *nur Frauen:* Ich bin nicht schwanger und stille nicht
- Ich habe keine offenen Wunden
- kein Morbus Raynaud
- keine Krampfadern
- keine akuten Herz-Kreislauferkrankungen
- keine arteriellen Durchblutungsstörungen
- kein Herzschrittmacher
- kein Bluthochdruck
- keine Schilddrüsenunterfunktion
- keine Epilepsie
- keine Tumore
- keine Immuntherapie
- keine chronischen Atemwegskrankheiten
- keine schwere Anämie
- keine schweren psychischen Erkrankungen
- kein Alkoholismus
- keine Drogen
- in den letzten sechs Wochen keine (systemischen) Immunsuppressiva, Kortikosteroide und andere Medikamente und Verfahren, die bei Neurodermitis nachweislich unterstützend wirken (wie Psychotherapie oder Lichttherapie)

Geschlecht: E-Mail:

Körpergröße:

Gewicht: Telefonnummer:

Unterschrift …….

Vielen Dank für Ihre Teilnahme!