EFFECTS OF BALNEOTHERAPY ON MUSCULOSKELETAL DISORDERS WITH CHRONIC PAIN

PhD Thesis

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Szeged, 2014

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PhD programme titled
Clinical and Experimental Research in Reactivating and Organ-Saving Surgery.
Clinical and experimental investigations into solutions
based on evidence for sustaining and reactivating articular functions

Supervisor: Tamás Bender MD, PhD, DSc

Szeged, 2014

ACKNOWLEDGMENTS

It is hard to express my heartfelt gratitude to my supervisor, professor Tamás Bender, for his invaluable support both professional and human which I received from him all along the years of my PhD work. His continued encouragement led me to the right way.

I particularly wish to thank Géza Bálint for having started me with my work. Any time I sought help from him, he was always there to give me guidance, which proved to be decisive.

My thanks also go to Gyula Gyetvai, Remény Horváth and András Koroknai for their respective institutional support enabling me to carry out my research.

My sincerest thanks to László Hodinka for his teachings.

My appreciation to Katalin Hodosi and András Németh for their statistical calculations and advices.

I am also grateful to Csaba Kovács, my „PhD companion", for the consultations and our joint works.

I thank my colleagues and especially Ramóna Gaál for our joint works. My special thanks go to the staff of the Rheumatology and Physiotherapy Department of the Józsefváros Health Care Services and particularly Mrs Péter Illés née Éva head assistant, Mrs Ferenc Kleiber née Judit, Klára Kovács and Ágnes Antal assistants, and Rakib Mohamed Badruddin, physiotherapist, for their contribution. My thanks also to Mrs Roland Kis née Tímea, assistant at Mofetta & Thermal Spa, Mátraderecske.

I also want to include in this list Margit Dubecz Kázmérné, head pharmacologist, for her contribution in producing the control pack for our doble blind study.

I am thankful to my grandparents and parents who allowed me to start my carreer. They guided me, supported me and loved me. My thanks to my sister, for everything.

I thank my partner for his patience, help and love, all along my doctoral years.

LIST OF PAPERS

included in the dissertation

I.

Tefner IK, Kovács Cs, Gaál R, Koroknai A, Horváth R, Badruddin MR, Borbély I, Nagy K, Bender T. The effect of balneotherapy on chronic shoulder pain. A randomized, controlled, single-blind, follow-up trial. A pilot study. Clin Rheumatol 2013 dec 17. [Epub ahead of print] **IF:2.07**

II.

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III.

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IV.

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V.

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CONTENTS

LITERARY OVERVIEW

Definitions

According to a proposal for a worldwide definition of health resorts medicine and balneology, balneotherapy has been defined as the use of natural mineral waters, natural peloids and mud, natural sources of different gases (carbon dioxide, hydrogen sulphide and radon) for medical purposes such as prevention, treatment, and rehabilitation. It can be implemented as head-out immersion or bathing of body parts in mineral water, peloids or gases; as the application of mud/peloid packs to body regions; as exposure to gases during bathing and by inhalation; or as by drinking mineral water [1].

Medical mineral waters require minimum concentrations of ions and/or gases, the thresholds of effective concentration should be defined on scientific evidence. The composition and threshold values may vary from country to country [1]. In Hungary, mineral water sourced from spontaneously springing or drilled wells contains at least 1,000 mg/L of minerals, or some of the important trace elements are present in the water in an increased concentration (e.g. sulfide or iodide ion >1 mg/L, bromide ion >5 mg/L, radon >1 millicurie/L). Mineral waters are classified by their chemical composition, such as salty, carbonated, and radioactive waters as well as waters containing calcium chloride, magnesium chloride, sodium hydrogen carbonate, calcium hydrogen carbonate, magnesium hydrogen carbonate, iron, iodides, bromide, sulfate, or sulfide (sulfur water) [2-5]. Waters can be described as hypothermal (<35˚C), isothermal (35-36˚C) and hyperthermal (>36˚C) [1]. In Hungary, a mineral water is called thermal water if its temperature is at least 20˚C from a spontaneously springing well or at least 30˚C from a drilled well. In Hungary, the name "medicinal water" is defined by the regulatory authority; a mineral water is declared as medicinal water if it meets certain microbiological criteria, and if its favorable effects are documented by clinical studies [2-5].

The use of plain water (tap water) for therapy or prevention is called hydrotherapy. Further core elements of health resort therapy interventions in health resorts are particularly climatotherapy, besides other interventions (e.g. physical therapy, psychotherapy, nutrition, occupational therapy) [1-3].

Medical muds/peloids have a high heat storage capacity; therefore they are mostly used warm. Muds/peloids are applied in the form of packs or bath, which may involve treatment of certain body parts or the whole body [1, 6-8]. Mud/peloid therapy is traditionally used for the treatment of musculoskeletal disorders in many European and non-European countries [6].

The international nomenclature and classification of muds/peloids are not consistent. According to a recent proposal muds/peloids are formed by the maturation of finely granulated organic and/or inorganic materials of natural origin (generated by geological and biological processes) and mineral water or salt water (from sea or salt water lakes) [9]. During maturation, metabolic processes of

the microorganisms produce organic components [6, 8-11], with probable anti-inflammatory effects [12-13], and some physical properties of the peloid such as particle size, heat storage capacity, rheological properties also change [10]. The authors also comment on the fact that the term peloid is a comprehensive term including natural peloid (formed by natural maturation) and peloid in a strict sense (formed by artificial maturation). Natural maturation takes place in the natural environment. Artificial maturation takes place in tanks during a variable time from less than 1 month to several years with a mixture of mineral water or sea water with fine-grained natural inorganic and/or organic materials, under defined conditions. Concerning peloid application, medical peloid (with therapeutic properties approved by authorities) and cosmetic peloid are also differentiated [9].

Musculoskeletal disorders with chronic pain relevant from balneological perspective and the dissertation

In the therapy of musculoskeletal disorders with chronic pain, especially in the therapy of degenerative musculoskeletal disorders, balneotherapy has been traditionally used and has been cultures being built on it for centuries and in different civilizations [2, 14]**.**

Osteoarthritis is the most common and most burdensome musculoskeletal disorder, and one of the most frequent causes of physical impairment. Osteoarthritis is a chronic disorder characterized by softening and disintegration of articular cartilage, with reactive phenomena such as vascular congestion and osteoblastic activity in the subarticular bone, new growth of cartilage and bone (osteophytes) at the joint margins, and capsular fibrosis. Recurrent synovitis, avascular necrosis of the subchondral bone, weakness of periarticular muscles, joint instability are modifiers that influence the rate of pathologic and clinical progression. The clinical pictures are heterogeneous in any particular joint. Joint involvement varies from a monarthritis through a pauciarticular arthritis involving only the large weight-bearing joints to a polyarthritis including the interphalangeal joints of the fingers. When osteoarthritis appears without any obvious antecedent insults to the joint, it is called “primary” or “idiopathic”, when it follows a demonstrable abnormality or injury, it is designated as “secondary”. The exact etiology of this multifactorial disease is unknown. The primary factors can be genetic, metabolic, or endocrine, which perhaps alter the physical properties of articular cartilage. The secondary factors, such us trauma, or eccentric stress, specify where and when osteoarthritis develops. Osteoarthritis is more common in some joints (the fingers, hip, knee and spine) than in others (the elbow, wrist, and ankle). This fluctuating disease ends up in anatomical and functional insufficiency of the joint, thus leads to impaired self-care functions and decreased quality of life [15-16].

International recommendations for management of osteoarthritis are often divided into three main categories: non-pharmacological, pharmacological and surgical [17]. According to a systematic review of recommendations and guidelines for the management of osteoarthritis including 16

articles published recently in 2014, for non-pharmacological modalities, education/self management, exercise, weight loss if overweight, walking aids as indicated, and thermal modalities were widely recommended. For appropriate patients, joint replacement was recommended. The most recommended pharmacologic modalities included acetaminophen/paracetamol in first line, and topical or oral non-steroidal anti-inflammatory drugs (NSAIDs) in second line. Intra-articular corticosteroids were generally recommended for hip and knee osteoarthritis [18]. In 2003, based on level B evidences, the European League Against Rheumatism (EULAR) recommended balneotherapy and hydrotherapy for osteoarthritis [19]. It is important to note, that in 2013 balneotherapy was not even mentioned in the analysed non-pharmacological treatments of knee osteoarthritis of EULAR recommandations [17]. According to the letters to the editor published after the EULAR reccomandations 2013, the explanation could be hypothesised that balneotherapy is not equally available and/or common in every country [20-21]. In the Osteoarthritis Research Society International (OARSI) Guidelines for Non-Surgical Management of Knee Osteoarthritis, balneotherapy was considered as an appropriate treatment for specific clinical subphenotypes with multiple joint osteoarthritis and comorbidities, based on systematic review and metaanalysis of randomized controlled trials (RCTs) [22].

Low back pain is a major health and socioeconomic problem. Low back pain is usually defined as pain, muscle tension, or stiffness localized below the costal margin and above the inferior gluteal folds, with or without leg pain (sciatica) [23]. Specific low back pain is defined as symptoms caused by a specific patho-physiological mechanism, such as hernia nuclei pulposi, infection, inflammation, osteoporosis, fracture, spondylolisthesis, or tumor. Non specific low back pain is defined as symptoms without clear specific cause (low back pain of unknown origin), which is approximately 90% of all low back pain patients. Low back pain is defined as acute when it persists for less than 6 weeks, subacute between 6 weeks and 3 months and chronic when it lasts for longer than 3 months [23]. Low back pain symptoms often fluctuate over time, most patients with low back pain will have experienced a previous episode, and acute attacks often occur as exacerbations of chronic low back pain [24]. Reported lifetime prevalence of low back pain varies between 49% to 70% [23-24]. 90% of patients with low back pain in primary care will have stopped consulting their doctor within 3 months. 5% of people with an acute episode of low back pain develop chronic low back pain and related disability [24]. The longer the period of sick leave the less likely return to work becomes. Less than half of the low back pain patients who have been off work for 6 months will return to work. After 2 years of absenteeism, the chance of returning to work is virtually zero. It is important to identify and treat those low back pain patients who are at risk for long-term disability and sick leave (individual, psychosocial and occupational factors) [23].

The other target is to reduce pain and to improve function in chronic low back pain. There is strong evidence that exercise therapy, behavioural therapy, and multidisciplinary pain treatment programs are effective for chronic low back pain [23]. There are some evidences about the

effect of brief educational intervention, cognitive behavior therapy, NSAIDS, analgesics, opioids, muscle relaxants, back schools in occupational settings, mobilisation, spinal manipulation, acupuncture, massage, anti-depressants and capsaicin [23-32]. Despite the fact that balneotherapy is traditionally and widely used in the treatment of chronic low back pain, the clinical recommendations do not mention balneotherapy as there is not enough evidence.

In addition to low back and neck pain, shoulder disease is the third most common musculoskeletal disorder patients seek medical care for [33]. The estimated yearly incidence of shoulder disease in the United States is up to 7%, its yearly prevalence in different countries is between 20% and 51%, and lifetime prevalence is approximately 10% in the average adult population. In 40% of patients attending primary health care for a new episode of shoulder pain, symptoms can last even up to 12 months [33-34]. The painful limitation of shoulder motion affects hand and arm motion as well, therefore it significantly influences work performance and everyday activities as well as the quality of life. Therefore, the treatment of patients with shoulder pain has major social and health economic implications [34-35].

The diagnosis and classification of shoulder disease is not uniform [33, 35]. Shoulder pain is caused by periarticular, glenohumeral, and regional (other than shoulder) disorders. The majority of painful nontraumatic conditions about the shoulder joint are caused by tendinitis of the rotator cuff. Degenerative tendinitis has been labeled e.g. subacromial bursitis, subdeltoid bursitis, supraspinatus tendinitis, impingement syndrome [34-36]. Biceps tendinitis is most often associated with other surrounding shoulder pathologies such as degenerative rotator cuff lesions and impingement syndrome as a secondary process. Primary tendinitis is rare and has been estimated to represent about 5% of the cases [37].

Treating shoulder disease is a challenge also. The aim of the treatment is to decrease pain and improve function [34]. Several accepted conservative treatment options exist for shoulder pain. These include pharmacotherapy (analgesics, NSAIDs, oral steroids, and steroid injections), physiotherapy (including exercise therapy and the application of physical modalities), mobilization, manipulation, and health education. In cases resistant for conservative therapy, hydrodilatation and surgery may be considered [34-36].

Due to the diagnostic and classification difficulties, no uniform, specific treatment protocol exists [34-36]. According to the meta-analysis of Gaujoux-Viala C, efficacy of local steroid treatment is equal to that of NSAIDs in the acute and subacute stage of shoulder tendinitis: compared to other treatments (physiotherapy, wait and see, placebo), it decreases pain and improves function. However, this effect is confirmed only in studies with short term, and no long-term benefit was shown [38].

Several systematic reviews and meta-analyses have proven the pain-reducing and function-improving effect of exercise treatment in chronic shoulder pain [39-42]. The efficacy of transcutaneous electrical nerve stimulation (TENS) in shoulder pain is not proved [43].

In some European and Asian countries, balneotherapy is traditionally and widely used in the treatment of chronic shoulder pain [1]. However, we have data only from one Turkish study showing the beneficial effects of hot mud packs in subacromial impingement syndrome [44]. The effect of mineral water bathing on chronic shoulder pain has not yet been studied.

We can conclude that the therapies recommended for the treatment of degenerative musculoskeletal disorders have their own limitations, including inadequate therapeutic effects and adverse effects. It is important to note that due to gastrointestinal side effects, pharmacological treatment (particularly NSAID therapy) has its limitations with significant financial and health economic consequences [45].

Evidence based medicine and balneotherapy

A therapeutic method is considered proven and recommended by evidence-based medicine if it has been applied on at least one randomized controlled trial (RCT) with an adequate number of patients and with appropriate methodology, and optimally is confirmed by the meta-analysis of several RCTs. The highest level is the randomized, controlled, optimally double-blind study [46]. There are many hindrances in studying the effects of balneotherapy. In most cases, it is difficult to make an appropriate control group. It is also challenging (sometimes impossible) to produce an appropriate placebo (e.g. tap water similar to mineral water, a material similar to mud, etc.). Therefore, the control group in balneology studies often consists of patients receiving other therapy or no treatment at all. Due to several reasons including a lack of interest from the pharmaceutical industry, financial problems may also arise, which makes it difficult to perform large scale studies. It is arduous to distinguish the specific effects of balneotherapy from other therapeutic factors such as climate effects, physical effects of hydrotherapy, or effects of aquatic exercise, etc. Optimally, the effects of balneotherapy are investigated in an outpatient setting and without disturbing the patient's normal lifestyle. The meta-analysis of balneotherapy studies performed so far is also complicated, since most of these studies included have heterogeneous patient populations, and the type, intensity, and duration of treatments, the methods used, and the time of assessments were not uniform. Finally, it has to be emphasized that balneotherapy is a traditional, empirical therapy, which did not require evidences before the evidence-based medicine era. In our opinion, the above listed facts might be the reasons for the contradiction that, in practice, balneotherapy is considered a traditional therapy, but it is not part of the international therapeutic recommendations.

Evidences on the effects of balneotherapy on musculoskeletal and non musculoskeletal diseases

There are truly limited evidences on the effects of balneotherapy on musculoskeletal and non musculoskeletal diseases based on metaanalysis and systematic reviews. In 2010 Kamioka et al. reviewed hydro- and balneotherapy papers published between 1990 and 2008. The authors could not draw any conclusions regarding balneotherapy because of the diversity of outcome measures, the absence of proper control groups, and poor study design [47]**.** Similarly, according to the systematic review of AP Verhagen et al. published in 2012, balneotherapy might be beneficial, but the evidence is yet insufficient to make a definitive statement about its use because of the methodological quality of the trials. In the individual studies balneotherapy seems to be beneficial for most patients, high quality trials are needed [48]. In 2009 Falagas et al. reviewed balneotherapy studies excluding hydrotherapy trials. They selected 29 RCTs of 1720 patients; 8 of these evaluated balneotherapy in osteoarthritis, 4 in fibromyalgia, 4 in ankylosing spondylitis, 4 in rheumatoid arthritis, 3-3 in psoriatic arthritis and in chronic low back pain, and one in Parkinson's disease. In 17 trials, pain decreased significantly compared with the control group, whereas in 8 trials there was no difference. The analgesic effect of balneotherapy lasted for 3 months in 9 studies of longer duration [49].

It is important to mention the beneficial effect of subaqual exercise on degenerative musculoskeletal diseases. The land based exercise pain reducing and function improving effect is proven by systematic reviews in osteoarthritis of the knee and in chronic low back pain [50]. The systematic review by Verhagen et al. published in 2012 concluded that aquatic therapy is probably effective in patients with osteoarthritis, low back pain and fibromyalgia in the short-term when compared to no treatment, nevertheless, it remains unclear wheather aquatic exercise are more effective than other active interventions such as land-based exercises. There is lack of evidence of specific doses and timing of exercise programmes [48].

Verhagen et al. in their meta-analysis of studies evaluating balneotherapy in osteoarthritis in 2008 found only a few well-designed trials using appropriate statistical methods. The authors concluded that the effect of balneotherapy is "unproven" and called for additional well-designed studies [51]. The systematic review by Forestier et al. published in 2008 led to a similar conclusion regarding balneotherapy trials of knee osteoarthritis. The small number of included patients and the poor methodology prevented any conclusions regarding the decrease of pain, improvement of function and quality of life following balneotherapy of patients with osteoarthritis of the knee [52]. Harzy et al. reviewed 9 RCT-s evaluating the effects of balneotherapy on knee osteoarthritis in 2009. They found that the pain measured by visual analogue scale (VAS) decreased significantly for 8-12 weeks in six and for 20-24 weeks in two RCTs; articular function also improved [53].

Several authors have described the significantly better effects of balneotherapy (immersion in mineral water) on pain, mobility, and quality of life compared to hydrotherapy (immersion in tap water with the same temperature as mineral water) in knee [54-58], and hand osteoarthritis [59] in a double-blind condition. This is the optimal way to assess the chemical effect of mineral water. The colour of the mineral water can be imitated when necessary. It is also optimal to conduct trials under ordinary, non-spa conditions, in local, ambulatory patients, keeping them in their everyday environment. Hungarian authors were the first to use balneotherapy with heated tap water as placebo control in a double blind controlled study [54].

In 2010, Forestier et al. published a multicenter RCT (conducted at 3 study sites) of 382 patients with knee joint osteoarthritis, which is important from a methodological point of wiew also. The control group received drugs, advices and exercised. The active group was treated with massage, underwater massage, mud packing and baths in thermal mineral water for 18 days in addition to drugs, advices and exercise. Balneotherapy was significantly superior than control treatment in improving pain and joint function measured by WOMAC, even after 6 months of follow-up [60].

Pittler et al. published their meta-analysis of 5 RCTs (of 580 patients) appraising the effect of balneotherapy in chronic back pain in 2006. Active treatment comprised complex balneotherapy in 5 RCTs, but only immersion in thermal mineral water in one RCT. The controls were patients on the waiting list for balneotherapy, and/or received drugs and exercised. The author rated the results as “encouraging” as regards the decrease of pain, and emphasized the need for further research [61]. Since 2005, two tap water-controlled RCTs have evaluated the effect of balneotherapy on chronic low back pain, and described the significantly better effects of balneotherapy on pain, mobility, and quality of life compared to hydrotherapy in chronic low back pain [62-63].

There were no RCT-s evaluating the effects of immersion in mineral water on fibromyalgia compared with immersion in tap water. In the studies, besides balneotherapy the patients received other kinds of treatments. According to the opinions of the metaanalysises and systematic reviews, the complex hidro- balneotherapy decreased pain and improved quality of life of fibromyalgia patients [64-66].

Systematic review or metaanalysis of RCTs evaluating the effects of balneotherapy on other musculoskeletal disorders, e.g. osteoarthritis of the hip, osteoarthritis of the hand, or shoulder pain, or on non musculoskeletal disorders, has not been published in the absence of RCTS or in the absence of enough RCTs.

Mud/peloid therapy

According to controlled human clinical studies performed so far, mud therapy has analgesic effect and causes long-term improvement of joint function in patients with knee osteoarthritis [67-73]. Combined with other treatments such as thermal mineral water baths [74-78], or applied in complex spa therapy [60], mud therapy has a positive effect not only on knee but

also on hand osteoarthritis [79]. Controlled clinical studies showed the beneficial effect of mud therapy also in rheumatoid arthritis [80-81]. Combined with thermal mineral water baths mud therapy had beneficial effect also in fibromyalgia [82], psoriatic arthritis [83-84], ankylosing spondylitis [85], and rheumatoid arthritis [86]. Applied in complex spa therapy, muds have a therapeutic effect also on chronic low back pain [87]. Mud therapy alone [70] or in combination with other treatments [74, 60] has been shown to have a favorable effect on the quality of life in patients with knee osteoarthritis.

A recently published review analyzed studies evaluating the effects of mud therapy on knee osteoarthritis. Of the 20 studies reviewed, pain decreased in 17 studies, function improved in 12 studies, and quality of life improved in 5 studies. The authors concluded that peloid therapy is an effective therapeutic modality in the treatment of knee osteoarthritis, though studies with a better methodological quality are needed [11].

Liu H et al. published their metaanalysis of seven studies with 410 patients in 2013. They concluded that mud therapy is a favorable option for pain relief in patients with knee OA, but additional high-quality randomized controlled trials need to be conducted [88].

Amongst the controlled clinical studies evaluating the effects of mud therapy in knee osteoarthritis, Mahboob et al. randomized 50 patients with knee osteoarthritis into two groups. In one group, patients received mud therapy, and in the other group, placebo gel packs (used by the authors as a vehicle for mud therapy) were applied. The patients received home treatment for 30 days. Significant improvement in the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain and stiffness score was observed in the mud-treated group only and there was a significant difference between the two groups after the treatment; WOMAC functional capacity improved in both groups [67].

Odabasi et al. compared the effect of mud pack and nylon-covered mud pack in 60 patients (randomized into two groups) with knee osteoarthritis. Outpatient treatment lasted 3 weeks. The temperature of the packs was 43°C. WOMAC score, pain, and the patient's and physician's assessment of disease status significantly improved by the end of treatment in both group and this was even more significant and lasted longer (for 6 months) in the mud-treated group. Analgesic consumption similarly and significantly decreased in both groups by the end of treatment but, after 6 weeks, this decrease remained significant in the mud-treated group only [68].

In the study of Evcik et al. involving 80 patients, Group 1 bathed in 38°C thermal mineral water, Group 2 received 42°C mud pack therapy, and Group 3 received 42°C hot pack therapy on 10 occasions for 2 weeks. WOMAC pain, functional capacity, and total scores as well as knee pain with walking significantly improved in all groups by the end of treatment, but this remained significant only in Groups 1 and 2 during the follow-up period; however, the difference between the groups was not significant at none of the assessments. VAS "pain at rest" score did not change in any of the groups. Certain dimensions (pain, mobility, sleep) of the

Nottingham Health Profile (NHP) questionnaire measuring quality of life improved by the end of treatment and during the follow-up period in Groups 1 and 2, but the changes were not significant in Group 3 [70].

In a study performed by Flusser D et al., one group (40 patients) received mud therapy, whereas the other group (18 patients) received mineral-depleted mud therapy. The patients received home treatment on 15 occasions for 3 weeks. A decrease in pain (by the end of treatment and during the follow-up period) and in the Lequesne Index of severity of knee osteoarthritis (at the end of treatment and 1 month after treatment) was observed only in the mud-treated group; however, long-term improvement of the Lequesne Index was observed only in the control group [71].

According to the study of Bostan et al. involving 23 patients with stage 2-3 knee osteoarthritis, bilateral intra-articular hyaluronic acid treatment and 45°C mud therapy applied weekly for 3 weeks had similar positive effects on pain and joint function [69].

In two Turkish studies, the effects of mud therapy and hydrocollator hot pack treatment were compared. In the study with 27 patients, Sarsan A et al. observed long-term and significant decrease in pain, joint function, interleukin 6 and insulin-like growth factor 1 levels only in the mud-treated group, and this decrease was significantly greater than in the control group [72]. In the study of Güngen G et al. involving 44 patients, long-term decrease in pain and joint stiffness was observed in both group after the treatment, but physical activity improved long-term only in the mud-treated group, in the hot pack group this was observed only by the end of treatment. Serum YKL-40 (also called human cartilage glycoprotein-39) level indicating cartilage degradation increased significantly only in the hot pack group 3 months after the treatment [73].

Clinical trials on the effect of mud therapy suggested its effectiveness on osteoarthritis of the knee [67-73], and some of them showed that it is more effective than the control treatment [67-68, 72].

Effects and mechanisms of action of hydro- and balneotherapy based on the existing evidences and hypotheses

In the course of mineral bath treatment, hydrotherapy exerts its effects. During immersion, the physical characteristics of the water cause physiological changes. Since the specific gravity of the human body considering adipose tissue is lower than that of water (and higher when considering bone, muscle, connective tissue, and organs, therefore it depends on the individual's physique), according to Archimedes' principle, an upward buoyant force is exerted on the body immersed into water. By eliminating gravity, this helps gradual mobilization in musculoskeletal pain and muscle weakness. Under hydrostatic pressure dependent on the specific gravity of the fluid and the depth of immersion, circulation becomes centralized, which increases cardiac output without increasing heart rate and exerts a diuretic effect via a reflex mechanism (stretch-

ing of the volume receptors increases the secretion of atrial natriuretic factor and decreases the secretion of antidiuretic hormone, which leads to natriuresis) [89-94]. Increased cardiac output enhances muscle blood flow from 1.8 mL/min/100 g tissue measured on land at rest to 4.1 mL/min/100 g tissue measured when immersed into water up to neck level, which means a 225% increase. During immersion, circulation of the deep muscle structures and oxygen supply of the tissues increase, which may facilitate the healing of muscle, joint, or bone injuries Viscosity is the internal friction of the fluid, resulting in resistance during movement. Viscous resistance is proportional to the force applied against it and is increased by turbulence. This emphasizes the role of hydrotherapy, including aquatic exercise, in muscle strengthening. The thermodynamic characteristics of water and mud are important, which means that the heat-retaining capacity and heat conduction of the water and mud is high, therefore, it is able to keep its temperature (warm or cold) and easily passes it to its environment [89-91].

The gate control theory of pain acting via heat receptors and mechanoreceptors has been described [95]. In response to heat, serum beta-endorphin levels increase together with pain decrease and euphoria suggesting the role of endogenous opioids [96]. Heat also increased serum cortisol and catecholamine levels, which may have an anti-inflammatory effect [97-98]. According to Becker BE et al., immersion in cool water produced a rise from baseline in sympathetic nervous system activity, with a drop in sympathovagal balance, which likely represents a physiologic stress response. Warm water immersion still produced a rise in sympathetic power (while smaller) with a small elevation in sympathovagal balance from baseline [90]. The elevation in sympathovagal balance is associated with stress reduction, positive emotions, relaxation, meditation, etc [90, 99]. A decrease in both mean blood pressure and diastolic pressures during the immersion period, most pronounced during the warm water cycle and subsequent to it was observed [90, 100-101]. Data exist that during water immersion, neuromuscular function is modified compared to the non-immersed control, however some results are inconsistent [102-103]. It is possible that in response to heat, elasticity of collagen-rich tissues increases, muscle spasm decreases, which presumably reduce pain, and joint function improves [91, 104]. After the application of the mud pack, increased blood circulation was observed by laser Doppler flowmetry [105]. It has been shown that during maturation of muds/peloids, colonizing microorganisms produce sulpho-glycolipids, which are thought to have anti-inflammatory effects [12-13]. It has already been reported that hydro- and balneotherapy have beneficial effects on anxiety, depression, and mood. It may also play a role in the alterations of pain experience and in the improvement of quality of life [106].

Mineral water and peloids may also have a specific chemical effect. The significantly better effects of balneotherapy on pain, mobility, and quality of life compared to hydrotherapy in knee [54-58], and hand osteoarthritis [59] and in chronic low back pain [62-63] might indicate an additional specific chemical effect of thermal mineral water resulting from its composition.

Inferring from other studies, balneotherapy modified the level of inflammatory mediators (e.g. interleukin-1 alpha, leukotriene B4, prostaglandin E2, tumor-necrosis-factor alpha, insulin-like growth factor 1, transforming growth factor beta) [91, 107], and had a positive effect on the markers of antioxidant status [108-111] and cartilage degradation (e.g. adiponectin, matrix metallopeptidase 3) [91, 111].

There is hardly any data about the transcutaneous absorption of mineral water components. In a trial, increased serum concentrations of bromine, rubidium, calcium, and zinc was detected in psoriatic patients after bathing in the Dead Sea [112]. Only few data exists about the absorption and chemical effects of mud components. In an in vitro study, Beer AM et al. showed that fulminic acid, ulmic acid, and humic acid (water-soluble mud components) pass through the skin and enhance smooth muscle contractility via alpha-2 adrenergic and D2 dopamine receptors [113]. According to other in vitro studies the chemical components of mud pass through the skin [114]. Besides, it has been shown that alteration of the thermophysical properties of the peloid is accompanied by maturation and by an increase in its organic matter content [10].

Assessment of the effects of balneotherapy and the tools of health assessment

Similarly to other diseases, health assessment in musculoskeletal disorders include past medical history, physical examination (with goniometer, tape measure, etc.), radiology assessments (radiograph, ultrasonography, etc.), laboratory diagnostics as well as disease-specific and general health questionnaires. Optimally, health assessment with questionnaires should be performed in an internationally standardized way by using validated questionnaires. Below I briefly describe the questionnaires used in my research.

The WOMAC Osteoarthritis Index

The WOMAC Osteoarthritis Index is a tri-dimensional, disease-specific, self-administered, health status measure. It probes clinically-important, patient-relevant symptoms in the areas of pain, stiffness and physical function in patients with osteoarthritis of the knee and/or hip. The index consists of 24 questions (5 pain, 2 stiffness, 17 physical function) and can be completed in less than 5 minutes. It is avaible in Likert, Visual Analogue and Numerical Rating scaling formats. In our studies we preferred the Likert format. For Likert numerical values are assigned to each of the five response categories (0=none, 1=mild, 2=moderate, 3=severe, 4=extreme). For each WOMAC dimension, a subscale score is calculated by simple summation of the assigned values scored on component items. Thus, the range of possible subscale scores for the three dimensions is as follows: pain=0-20, stiffness=0-8, physical function=0-68. For convenience these scores can be normalised, and expressed on 0-10 or 0-100 scales, we preferred the last one. The minimum perceptible clinical improvement (MPCI) for

the WOMAC Index was proposed the following values: WOMAC Pain=9.7 nu, WOMAC Stiffness=10 nu, WOMAC function=9.3 nu. The proposed absolute (and relative) Minimal Clinically Important Improvement (MCII) for knee and hip osteoarthritis are between others as follows: -19.9 mm (-40.8%) and -15.3mm (-32%) for VA pain, -9.1 (-26%) and -7.9 (-21%) for WOMAC function subscale score [115-118]. The questionnare is validated in Hungarian [119].

The Oswestry Disability Index

The Oswestry Disability Index (ODI) is one of the most commonly recommended condition specific outcome measure for spinal disorders. The ODI has been published in at least four formats in English, the authors recommend the use of version 2. The index consists of 9 questions with 6 statements. For each section of six statements the total score is 5, if the first statement is marked the score=0, if the last statement is marked it=5. Intervening statements are scored according to a rank. Score is calculated as follows: (total score/(5 x number of questions answered)) x 100. The minimum difference in mean scores between groups that carried clinical significance was reported 4 points. A minimum 15-point change was reported in patients who undergo spinal fusion before surgery and at follow-up, more work is needed. The ODI is validated in Hungarian [120-121].

The Shoulder Pain and Disability Index (SPADI)

The SPADI was developed to measure current shoulder pain and disability [122-123]. Initially it was tested in a mix diagnosis group of patients reporting shoulder pain [122], and has since been used, among others, in rotator cuff disease [123].

The SPADI is a self-report questionnaire. It consists of 13 items in 2 subscales: 5-item subscale that measures pain and 8-item subscale that measures disability. The original version has each item scored on a visual analogue scale and a second version has items scored on a numerical rating scale (NRS). We preferred the latter version. The subscales are scored in a 3-part process. First, item scores within the subscale are summed. Second, this sum is devided by all items of the subscale to which the person responded. Third, this ratio is multiplied by 100 to obtain a percentage. Higher scores on the subscale indicate greater pain, and greater disability. To obtain a total score, all item scores are summed and divided by all items of the subscale to which the person responded. The minimal clinically important difference has been reported to be 8 points, and the minimal detectable change (MDC 95%) is 18 points [122-123]. Cross-culturally adaptation of the SPADI from English into Hungarian, and testing the reliability, and validity of the Hungarian version was done the first time parallel with the randomised, controlled, single blind, follow-up, pilot study evaluating the effect of balneotherapy on chronic shoulder pain [124].

The EuroQoL five dimensions questionnaire (EQ-5D)

EQ-5D is a standardised measure of health status developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal. The EQ-5D consists of two parts: the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS). The EQ-5D descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 3 levels: 1=no problems, 2=some problems, 3=extreme problems. A unique health state is defined by combining 1 level from each of the five dimensions. A total of 243 possible health states is defined in this way, each state is referred to in terms of a 5 digit code. EQ-5D health states, defined by the EQ-5D descriptive system, can be converted into a single summary index by applying a formula. The EQ VAS records the respondent's self-related health on a vertical, visual analogue scale where the endpoints are labelled 'Best imaginable health state' and 'Worst imaginable health state' [125].

Short Form (36) Health Survey quality of life questionnaires (SF-36)

The SF-36 is a multi-purpose, short-form healt survey with 36 questions. It includes 8 multi-item scales containing 2 to 10 items each plus a single item to compare the person's current health with their health 1 year earlier. The scales cover the dimensions of physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional and mental health. All items pertaining to each scale (excluding health transition) are summed and transformed to form a scale from 0 to 100, in which a higher score indicates a better state of health or well-being. The Version 2.0 of the SF-36, opposite to the Version 1.0 of the SF-36, include five-level response choices in place of dischotomous response choices for seven items in the two role functioning scales, and, five-level (in case of six level) response categories to simplify items in the Mental Health and Vitality scales. National calibration studies assured the comparability of average scores across Version 1.0 and 2.0 [126]. The SF-36 is validated in Hungarian [127].

Based on the above, it can be concluded that there is an urgent need for studies evaluating the effects of balneotherapy with adequate methodology. The aim of my work was to evaluate the effects of balneotherapy on musculoskeletal disorders with chronic pain, especially with degenerative origin, by performing studies with appropriate methodology and thus help balneotherapy to take its place in evidence-based medicine and in therapeutic recommendations.

Aims of the thesis

I. To evaluate the effects of immersion in mineral water on musculoskeletal diseases with chronic pain, especially with degenerative origin.

I./1. To evaluate the effects of immersion in high-mineral-content water from Mátraderecske on chronic low back pain compared to the control group treated with tap water.

I./2. To evaluate the effects of immersion in mineral water on chronic shoulder pain compared to the control group.

II. To evaluate the effects of mud/peloid pack therapy on muskulosceletal diseases with chronic pain, especially with degenerative origin.

II./1. To evaluate the effects of Neydharting hot mud pack therapy on osteoarthritis of the knee compared to an artificially produced control pack therapy.

II./2. To evaluate the effects of Kolop peloid hot pack therapy on osteoarthritis of the knee compared to the control treatment.

III. To undertake a systematic review and to conduct a meta-analysis of the trials by Hungarian authors in the field of balneotherapy meeting the predefined criteria.

THE EFFECTS OF SPA THERAPY IN CHRONIC LOW BACK PAIN. A RANDOMIZED-CONTROLLED, SINGLE BLIND, FOLLOW-UP PILOT STUDY

Objectives

As mentioned in the Literary overview, since the meta-analysis of Pittler et al. rated the results as only "encouraging" [61], two tap water-controlled RCTs have showed the beneficial effect of balneotherapy on clinical parameters in patients with chronic low back pain [62-63]. The beneficial effect of hidro- and balneotherapy on quality of life in patients with chronic low back pain has been also reported [63, 128].

The primary objective of our research was to ascertain whether the beneficial effect of high-mineral-content water from Mátraderecske spa could be demonstrated on clinical parameters in comparison to tap water, similar to the mentioned previous two tap water controlled studies. Our secondary aim was to evaluate whether the positive change of clinical condition would translate into a better quality of life and reduced analgesic and NSAID requirements versus baseline, as well as to assess the magnitude of these improvements in comparison to the control group treated with tap water.

Protocol and study parameters

Design

In this randomized (1:1), controlled, single-blind, follow-up study, we evaluated the effects of high mineral content water of Mátraderecske on chronic low back pain.

Participants

The study was conducted at the Mofetta and Thermal Spa in Mátraderecske, Hungary.

Patients with the following conditions were enrolled to the study: ambulatory patients from the catchment area, with chronic low back pain not complicated by severely restricted mobility; males and females aged 40 to 79 years; non-specific low back pain pre-existing since 12 weeks or longer, with evident tenderness of paravertebral muscles and painful limitation of motion of the lumbar spine; behind the chronic low back pain suspected, segmental limitation of motion, segmental instability or other underlying cause associated with radiologically confirmed or not confirmed spondylosis, discopathy, or spondylarthritis; severity of low back pain on exertion, expressed as a VAS score of 35 mm or greater (on a 100-mm visual analogue scale); lack of systemic or topical treatment with steroids, physical or balneotherapy within 2 months of inclusion, but exercise therapy was allowed.

Exclusion criteria were: acute low back pain; organic neurological deficit associated with lumbar pain; suspected vertebral compression of osteoporotic or other aetiology; underlying malignancy; pain resulting from inflammatory spine disease; spondylolisthesis (Grade 2 or higher); history of spine surgery; general contraindications to balneotherapy.

The study participants were patients under regular outpatient care recruited according to the study protocol by the rheumatologist of the Mofetta and Thermal Spa in Mátraderecske. The study was implemented between May 2010 and November 2010. Balneotherapy was performed at the Mátraderecske Spa, hydrotherapy took place at the Mofetta and Thermal Spa in Mátraderecske in a tap water content pool.

Study participants received written information and signed an informed consent form before the study. The study was approved by the regional ethics committee (approval number: 20822-1/2012).

Intervention

Fifteen 30-minutes-long balneotherapy sessions were administered over 3 weeks, 5 days a week, using either mineral water in the treatment group or tap water in the control group of 31 °C temperature. In both pool – each one with 1 meter of depth – the participiants had the possibility either to sit on seats or to move in a half-sitting or squatting position or to swim, which meant that the patients didn't experience cold. Patients knew which type of water they were using, as it was unfeasible to imitate the properties of mineral water (**Photo 1)**.

Balneotherapy was carried out with mineral water from the spring of Mátraderecske. The mineral water used in this study was of extremely high mineral content with a total mineral substance of 10900 mg/L, characterized by the dominance of sodium, hydrogen carbonate and chlorine, also containing abundant quantities of sulphate, magnesium and metaboric acid (**Table 1).** Mátraderecske is a small village in Northern Hungary. The natural resources of this area also include the only mofetta (volcanic gas eruption) of the country, which is being utilized for therapy with dry carbon dioxide. The treatment of the control group was carried out with tap water.

Outcomes

Appraisal was performed before the first and after the 15th balneotherapy session (on Week 0 and 3), as well as 3 and 10 weeks after the end of the balneotherapy course (on Week 6 and 13). On these occasions the VAS scores of lumbar pain at rest and on exertion were recorded, physical examination was performed, including Schober's test for mobility of the lumbar spine, as well as of the range of lateral flexion of the lumbar spine in both directions (in centimetres) [129]. Additionally, the disease-specific Oswestry Disability Index, as well as the EuroQol-5D and SF-36 questionnaires pertinent to quality of life were taken. Daily and

weekly consumption of analgesics and NSAIDS, taken to relieve chronic lumbar pain was recorded one month before as well as during the study and the follow-up period.

Randomization and blinding

The person randomizing the patients used a computer program for the randomization. He received patient information via e-mail. Following randomization, a professional not involved in the study enrolled the patients followed-up at the regional rheumatology outpatient clinic into either of the two groups. The condition of study subjects was appraised before and after the balneotherapy course, as well as during follow up by a single independent investigator unfamiliar with the treatment received by the examined patients. The physician supervising the treatment was available during balneotherapy sessions. Statistical analysis was performed by an independent person.

Statistical methods

Data were analyzed with Microsoft Excel software. Statistical comparisons were made using single-sample (paired) and two-sample *t*-tests. The significance value was 0.05. An intention-to-treat (ITT) analysis was performed.

Results

60 patients were randomized in equal proportions to treatment with mineral water (n=30, mean age: 63.57±8.6 years) or tap water (n=30, mean age: 64.33±6.6 years). Sex distribution of the study population was 14 males and 46 females. At baseline, there were no substantial differences between the two patient groups as regards their demographical and study parameters.

Following randomization, three subjects declined treatment before the start of the balneotherapy. Therefore, the treatment group (using mineral water) comprised 30, whereas the control group (using tap water) consisted of 27 patients.

The number of patients lost to follow-up was 13 in the treatment and 7 in the control group. In the treatment group, two patients were excluded at Visit 2: one owing to the lack of compliance and another because of abdominal surgery; at Visit 3, additional six patients were withdrawn owing to the lack of compliance; finally, three patients were excluded at Visit 4 for upper airway infection and additional two for lack of compliance. In the control group, one patient was excluded for the lack of compliance at Visit 2 and additional three at Visit 3, whereas one patient was withdrawn for upper airway infection and further two for lack of compliance at Visit 4. Fourteen excluded patients submitted completed questionnaires: nine in the treatment group (one at Visit 2, five at Visit 3 and three at Visit 4) and five in the control group (one at Visit 2, three at Visit 3, and one at Visit 4). These were processed and data from every study subject were used for the intention-to-treat analysis.

By the end of the balneotherapy course, the VAS score of low back pain at rest and on exertion, mobility of the lumbar spine (reflected by lumbar Schober's sign and lateral flexion in both directions), and the Oswestry Disability Index improved significantly in the treatment group, compared to baseline. These improvements persisted until the end of follow-up (as ascertained 3 and 10 weeks after the end of balneotherapy). By contrast, no significant changes occurred in the control group. Between-group differences in the above parameters were significant both at the end of balneotherapy and during follow-up.

In the treatment group, improvement of the quality of life measured by EuroQol-5D index compared to baseline was significant at the end of balneotherapy and for three subsequent weeks of follow-up. Reverse trends were observed for control subjects. The difference between the values measured in the two groups was significant at the end of balneotherapy and throughout the follow-up period (both at 3 and at 10 weeks after the end of the balneotherapy course).

The VAS score indicating overall health condition improved significantly in the treatment group by the end of balneotherapy and this improvement remained significant versus baseline until the end of follow-up. In the control group, significant deterioration was observed. The difference between the two groups was significant both at the end of balneotherapy and during follow-up.

By the end of the balneotherapy course, all components of the SF-36 questionnaire assessing health-related quality of life showed a tendency for improvement in the treatment group and – except for the components indicative of general health and social functioning – this improvement was significant in comparison to baseline. A reverse tendency, which was significant also for these two SF-36 components, was observed in the control group. The difference between the two groups was significant for every component at the end of balneotherapy. This difference remained significant for the majority of components until the end of follow-up (the exceptions were the SF-36 component pertaining to vitality at 3 weeks, as well as the components measuring physical role and social functioning at 10 weeks of follow-up).

In the treatment group, the consumption of analgesics and NSAIDs necessary to relieve chronic low back pain decreased significantly by the end of balneotherapy and this reduction remained significant (compared to baseline) until the end of follow-up. No significant change could be observed in the control group. The difference between the two groups was not significant at any time point **(Table 2)**.

Discussion

According to the results of our study immersion in mineral water of Mátraderecske may have a beneficial effect on the clinical parameters and quality of life of patients with chronic low back pain. Immersion in mineral water provided better results regarding pain, function and quality of life in patients with chronic low back pain than immersion in tap water, notwithstanding the statistical power of the study was low. Regarding the control group significant improvement was not observed.

In our opinion, the greater improvement in the treatment group can be explained in part by the mineral content of the water, which is extremely high, and by the fact that the patients knew which treatment they were receiveing. Some parameters worsened in the control group. This might be explained by the fact that the participants had seasonal work at that time on fields which accentuated their pain. This worsening was not observed in the treatment group. Single-blind design is one of the limitation of the study; however, it was not possible to imitate the properties of thermal mineral water in order to produce a suitable placebo. Moreover, controlling for the influence of additional therapeutic interventions not prescribed by the study protocol is still questionable.

This chapter was published during my PhD work.
With kind permission from Springer Science+Business Media:
Tefner IK, Németh A, Lászlófi A, Kis T, Gyetvai G, Bender T. The effect of spa therapy in chronic low back pain: a randomized controlled, single-blind, follow-up study. Rheumatol Int 2012; 32:3163-69.

Sodium	**Na^+**	**2800 mg/L**
Potassium	**K^+**	**96 mg/L**
Lithium	**Li^+**	**6.9 mg/L**
Calcium	**Ca^{2+}**	**78 mg/L**
Magnesium	**Mg^{2+}**	**170 mg/L**
Total hardness	**CaO**	**500 mg/L**
Ammonia	**NH_4^+**	**10.2 mg/L**
Metaboric acid	**HBO_2**	**44 B mg/L**
Chlorine	**Cl^-**	**1860 mg/L**
Sulphate	**SO_4^{2-}**	**640 mg/L**
Hydrogen carbonate	**HCO_3^-**	**4728 mg/L**
Bromide	**Br^-**	**9.4 mg/L**
Iodine	**J^-**	**0.85 mg/L**
Fluoride	**F^-**	**0.86 mg/L**
Total mineral substance		**10900 mg/L**

Table 1 The mineral composition of the mineral water of Mátraderecske

		Visit 1 (baseline)		Visit 2 (Week 3)			Visit 3 (Week 6)			Visit 4 (Week 13)		
		Mineral water, n=30	Control n=27	Mineral water, n=30	Control n=27	Between-group difference	Mineral water, n=30	Control n=27	Between-group difference	Mineral water, n=30	Control n=27	Between-group difference
		mean (SD)	mean (SD)	mean (SD) nature of change	mean (SD) nature of change		mean (SD) nature of change	mean (SD) nature of change		mean (SD) nature of change	mean (SD) nature of change	
VAS score of lumbar pain at rest (mm)		34.83 (27.6)	40.37 24.3)	19.83 (21.9) *p<0.01*	39.85 (25.4) *NS*	***p<0.01***	19.83 (21.8) *p<0.01*	43.63 (23.7) *NS*	***p<0.01***	20.17 (24.6) *p<0.01*	41.41 (27.2) *NS*	***p<0.01***
VAS score of lumbar pain on exertion (mm)		69.80 (17.5)	71.41 (18.5)	48.50 (18.5) *p<0.01*	72.0 (17.2) *NS*	***p<0.01***	48.60 (17.9) *p<0.01*	72.0 (17.6) *NS*	***p<0.01***	49.40 (22.4) *p<0.01*	71.63 (18.0) *NS*	***p<0.01***
Oswestry's Index		39.51 (18.0)	40.43 (15.2)	30.31 (17.6) *p<0.01*	40.51 (15.2) *NS*	***p<0.05***	28.38 (17.8) *p<0.01*	41.69 (15.9) *NS*	***p<0.01***	29.24 (17.1) *p<0.01*	41.70 (16.8) *NS*	***p<0.01***
Schober's sign		3.88 (0.9)	3.98 (1.1)	5.28 (0.9) *p<0.01*	3.94 (1.3) *NS*	***p<0.01***	5.40 (0.9) *p<0.01*	3.98 (1.3) *NS*	***p<0.01***	5.18 (1.1) *p<0.01*	4.02 (1.2) *NS*	***p<0.01***
Lateral flexion of the lumbar spine, to the right, (cm)		9.12 (3.6)	9.78 (3.1)	12.35 (3.3) *p<0.01*	9.72 (3.1) *NS*	***p<0.01***	12.50 (3.4) *p<0.01*	9.61 (2.9) *NS*	***p<0.01***	11.08 (3.6) *p<0.01*	9.11 (3.4) *NS*	***p<0.05***
Lateral flexion of the lumbar spine, to the left, (cm)		9.12 (3.5)	10.0 (3.1)	12.45 (3.7) *p<0.01*	10.15 (2.9) *NS*	***p<0.05***	12.88 (3.7) *p<0.01*	10.11 (2.9) *NS*	***p<0.01***	12.10 (4.0) *p<0.01*	10.04 (3.2) *NS*	***p<0.05***
EQ-5D index		0.54 (0.25)	0.504 (0.26)	0.637 (0.23) *p<0.01*	0.401 (0.34) *NS*	***p<0.01***	0.643 (0.24) *p<0.01*	0.390 (0.33) *p<0.05*	***p<0.01***	0.595 (2.78) *NS*	0.423 (0.30) *NS*	***p<0.05***
VAS score of perceived overall health status, (mm)		47.50 (13.6)	53.19 (14.7)	62.17 (15.2) *p<0.01*	49.30 (14.5) *p<0.05*	***p<0.01***	62.33 (16.2) *p<0.01*	49.26 (14.3) *p<0.01*	***p<0.01***	62.50 (18.0) *p<0.01*	49.44 (14.2) *p<0.01*	***p<0.01***
Analgesic and NSAID requirement, tablets/ week		5.83 (6.9)	4.74 (5.9)	4.37 (6.3) *p<0.05*	4.48 (5.6) *NS*	***NS***	4.10 (6.2) *p<0.05*	4.48 (5.6) *NS*	***NS***	3.73 (6.6) *p<0.05*	4.81 (6.01) *NS*	***NS***
SF - 36	Physical Functioning	34.50 (19.7)	36.67 (20.2)	49.33 (16.6) *p<0.01*	34.63 (18.8) *NS*	***p<0.01***	51.83 (18.5) *p<0.01*	33.89 (19.2) *NS*	***p<0.01***	50.33 (19.7) *p<0.01*	29.81 (18.9) *NS*	***p<0.01***
	Role-Physical	2.71 (5.6)	2.08 (3.0)	8.75 (9.2) *p<0.01*	1.85 (4.2) *NS*	***p<0.01***	9.58 (9.1) *p<0.01*	1.62 (5.4) *NS*	***p<0.01***	6.88 (9.8) *p<0.05*	3.01 (6.1) *NS*	***NS***
	Bodily Pain	35.67 (16.3)	36.76 (18.5)	52.17 (19.3) *p<0.01*	34.72 (15.0) *NS*	***p<0.01***	54.25 (19.9) *p<0.01*	35.83 (25.1) *NS*	***p<0.01***	46.83 (21.2) *p<0.01*	31.30 (19.5) *NS*	***p<0.01***
	General Health	33.06 (13.8)	33.02 (15.0)	35.14 (15.0) *NS*	26.54 (13.3) *p<0.05*	***p<0.05***	38.47 (15.8) *NS*	26.70 (16.0) *p<0.05*	***p<0.01***	37.36 (15.4) *NS*	26.08 (15.2) *p<0.05*	***p<0.01***
	Vitality	36.50 (20.2)	39.26 (18.8)	50.17 (22.0) *p<0.01*	35.74 (18.5) *NS*	***p<0.05***	47.67 (22.9) *p<0.01*	36.11 (24.1) *NS*	***NS***	47.83 (24.3) *p<0.01*	32.96 (20.7) *NS*	***p<0.05***
	Social Functioning	60.42 (27.7)	68.52 (18.5)	67.50 (23.6) *NS*	52.78 (24.4) *p<0.01*	***p<0.05***	67.50 (26.0) *NS*	50.0 (26.2) *p<0.01*	***p<0.05***	60.42 (27.3) *NS*	48.15 (28.3) *p<0.01*	***NS***
	Role-Emotional	6.94 (9.0)	7.10 (10.3)	12.50 (11.5) *p<0.01*	5.56 (9.2) *NS*	***p<0.05***	12.50 (10.7) *p<0.05*	4.01 (7.8) *p<0.05*	***p<0.01***	12.22 (11.7) *p<0.01*	4.63 (9.3) *NS*	***p<0.01***
	Mental Health	56.13 (26.4)	54.67 (20.6)	68.27 (23.6) *p<0.01*	49.19 (21.7) *NS*	***p<0.01***	62.27 (25.0) *NS*	46.81 (22.6) *p<0.05*	***p<0.05***	60.93 (27.6) *NS*	44.59 (26.6) *p<0.05*	***p<0.05***

Table 2 Study parameters and their changes versus baseline after immersion in mineral water of Mátraderecske and in tap water in patients with chronic low back pain, and the between-group differences

THE EFFECT OF BALNEOTHERAPY ON CHRONIC SHOULDER PAIN. A RANDOMIZED, CONTROLLED, SINGLE-BLIND FOLLOW-UP TRIAL. A PILOT STUDY

Objectives

The effect of mineral water bathing on chronic shoulder pain has not yet been studied. Therefore, the aim of our study was to investigate the effects of balneotherapy on chronic shoulder pain. Our primary objective was to find out whether balneotherapy has an adjuvant beneficial effect on the clinical parameters of patients suffering from chronic shoulder pain compared to the control group. Our secondary objective was to evaluate the effect of clinical improvement on the quality of life from the baseline and compared to the control group.

Protocol and study parameters

Design

In this randomized, controlled, follow-up study, we evaluated the effects of balneotherapy plus exercise versus exercise alone on chronic shoulder pain in two patient groups. Both groups received TENS treatment, as probably a placebo for shoulder pain in lack of evidence.

Participants

This study was conducted at the Department of Rheumatology and Physiotherapy of the Józsefváros Health Care Services in Budapest (Centre 1) and at the Musculoskeletal Rehabilitation Centre in Mezőkövesd (Center 2), Hungary.

Patients with the following criteria were enrolled to the study: outpatients with chronic shoulder pain; men and women between 30 and 75 years of age; complaints present for at least 2 months; at least mild shoulder pain (25 on the VAS scale) on movement; tenderness along the short or long head of the biceps brachii muscle possibly causing the complaints.

Before enrollment, anteroposterior comparative shoulder X-ray and shoulder ultrasound examinations were performed.

Exclusion criteria were: acute shoulder pain; rotator cuff tear; glenohumeral disorders (inflammatory arthritis, osteoarthritis, osteonecrosis, cuff arthropathy, septic arthritis, adhesive capsulitis, glenohumeral instability), regional disorders (e.g. cervical radiculopathy, brachial neuritis, nerve entrapment syndrome, sternoclavicular arthritis, reflex sympathetic dystrophy, neoplasms); shoulder pain probably caused by internal organ disease; previous shoulder surgery; previous shoulder fracture; complaints caused by obvious trauma; application of local steroid injection on the shoulder within 3 months prior to the study treatment

and within 1 months prior to the study treatment on other body parts; balneotherapy within 2 months prior to the treatment; general contraindications of balneotherapy; TENS therapy was allowed up to two weeks prior to treatment; exercises were allowed.

The study participants were patients under regular outpatient care recruited according to the study protocol by the rheumatologists of the Józsefváros Health Care Services in Budapest and the Musculoskeletal Rehabilitation Centre in Mezőkövesd. Exercise therapy and TENS therapy were performed at the local Physiotherapy Department. Balneotherapy took place at the Budapest Spa Plc. Széchenyi Spa in Budapest and at the Zsóry Spa in Mezőkövesd. Study participants received written information and they signed an informed consent form before the study. The study was approved by the Scientific and Research Ethics Committee (TUKEB).

Intervention

One group received individual, physiotherapist-led exercise therapy and TENS therapy for painful shoulder joint 2 to 3 times a week for 4 weeks on a total of 10 occasions, and the other group received the same treatment plus balneotherapy. Balneotherapy involved bathing in a 120-cm deep, 32°C water for 4 weeks in a total of 15 sessions, for 30 minutes per occasion. During balneotherapy sessions, patients were allowed to move, swim, stand, and sit in the water. Both mineral waters contain a significant amount of sodium, calcium, hydrogen carbonate, and sulphate.

The therapists who supervised the exercise were trained. Exercise therapy was performed on the basis of an agreement reached prior to the study between the physiotherapists and was adjusted to the individual status of the patient. Exercises included passive mobilization, gradual introduction of active exercises (muscle strengthening, joint mobilization), and active joint exercises taking into account the patient's actual range of motion. Patients received educational material, which included advices and a series of exercises to be done at home for at least 5 days a week. TENS was applied on the anterior and posterior aspects of the joint for 15 minutes with a mean frequency of 100 Hz and with 15 mA amplitude.

Adherence of patients to the treatment was registered in a checklist signed by the physicians on each occasion. The signed checklist of balneotherapy was controlled by the rheumatologists supervising the balneotherapy after the last balneotherapy session (one person in each center), and the signed checklist of the exercise and TENS was contolled at Visit 2 (one person in each center). The patients were asked not to have any other concomitant treatments, and if they had, they were asked to report it at the visits.

Outcomes

Disease assessment was performed before treatment (Week 0), after the last treatment session (Week 4), then 3 and 10 weeks after the end of treatment (Week 7 and Week 14, respective-

ly). Disease assessments included, as the primary objective, the evaluation of the VAS pain scores on movement and at rest, and the completion of the SPADI questionnaire [122-123]. As secondary objective the completion of the SF-36 and EuroQol-5D quality of life questionnaires were performed. All questionnaires were self-reported. Active shoulder girdle range of motion and passive glenohumeral range of motion were measured by a goniometer and the results were recorded. The assessors were trained. Both assessors (each one in each center) carried out examinations on the basis of an agreement reached prior to the study. In addition to the above, a detailed medical history was taken at each visit. At the same time, inclusion and exclusion criteria were checked, and possible side effects were recorded.

Randomization and blinding

Randomization was stratified by each center, separated, and a random number order was made. After randomization, an independent person assigned the patients to the appropriate group. The independent investigators blinded to the treatment on the basis of an agreement reached prior to the study examined the patients before treatment, at the end of treatment, and during the follow-up visits. As the patient cannot be blinded for the treatment, they were expressly asked not to tell the assessor in which group they were treated. The patients were examined by the same physician, which means one person in each center.

The independent physicians supervising the treatment were available during the treatments and they observed the possible side effects. The side effects of balneotherapy were supposed to be evaluated by the physicians supervising the treatments and finally by the rheumatologists working in the baths (1 person in each center) by means of a list (a blank sheet) on which, in case of the emergence of any side effect, the emergence was indicated (description of the side effect). The side effects of physiotherapy were evaluated by the physicians and finally by the rheumatologists supervising the treatments (one person in each center) by means, again, of a list (a blank sheet) on which, in case of the emergence of any side effect, the emergence was indicated (description of the side effect). Statistical analysis was performed by an independent person.

Statistical analysis

Statistical analysis was performed by using IBM SPSS Statistics 20. Distribution was assessed by the Kolmogorov-Smirnov test. Nonparametric methods were used in statistical calculations, due to the sample size. Data were analyzed by Mann-Whitney test and Friedman test. Bonferroni correction was made, the level of significance was calculated by dividing 0.05 by the number of the independent variables in the tests. So, the level of significance given by Bonferroni correction was 0.025 for VAS pain scores on movement and at rest, for SPADI and for EuroQuol-5D quality of life questionnaires, the level of significance given

by Bonferroni correction was 0.006 for SF-36 quality of life questionnaires, and 0.005 for clinical examination (active shoulder girdle range of motion and passive glenohumeral joint range of motion). The effect sizes between the two groups were estimated with a 95% confidence interval (CI). Regarding the Friedman test, the concordance was calculated and given by Kendall's coefficient (w). The results were evaluated by intention-to-treat analysis.

Results

54 patients were assesed for eligibility, 4 patients did not meet inclusion criteria, 4 patients declined to participate. Forty-six patients were randomized: 23 patients to the balneotherapy group (20 patients in Center 1, 3 patients in Center 2), and 23 patients to the control group (20 patients in Center 1, 3 patients in Center 2).

This study was conducted between December 2010 and June 2013. The patients were recruited continuously from December 2010 to March 2013. Participiants attended visits at baseline, at week 4., 7., and 13.

Patients participated in at least 80% of the treatment sessions. During the follow-up period, one patient in the balneotherapy group required periarticular steroid therapy for increasing pain at Visit 3 and therefore this patient was excluded from the study. Due to issues with compliance, one patient in the balneotherapy group and four patients in the control group did not attend Visit 4. No side effects were observed during the treatment period or the follow-up period. All patient data were analyzed according to the intent-to-treat principle. The statistical analysis performed was planned, no other statistical analysis was performed.

At the beginning of the study, the demographic characteristics and measured parameters of the two groups were comparable. This study included 17 male and 29 female patients. The average age was 59.7±8.3 years and 57,4±11.1 years in the balneotherapy group and in the control group, respectively.

Tenderness was noted in all patients along the initial segment of the long head of the biceps brachii muscle. In 30 of the 46 patients (17 patients in the balneotherapy group and 13 patients in the control group), ultrasonography confirmed tendovaginitis of the long head of the biceps brachii muscle. Ultrasound examination showed rotator cuff tendinopathy in 12 patients (9 patients in the balneotherapy group and 3 patients in the control group), and chronic subacromial bursitis and/or subdeltoid bursitis in 13 patients (5 patients in the balneotherapy group and 8 patients in the control group). Physical examination revealed impingement syndrome in 17 patients (8 patients in the balneotherapy group and 9 patients in the control group). Out of these patients, ultrasonography showed rotator cuff tendinopathy in 6 patients (4 patients in the balneotherapy group and 2 patients in the control group), chronic subacromial bursitis and/or deltoid bursitis in 6 patients (1 patients in the balneotherapy group and 5 patients in the control group), and

long head tendinopathy of the biceps brachii muscle in 9 patients (7 patients in the balneotherapy group and 2 patients in the control group).

The SPADI total pain, total disability, and total scores significantly improved from baseline to the end of treatment in both groups, and further improvement was observed during the follow-up period. The improvement was greater in the balneotherapy group. A significant difference was seen between the two groups in the SPADI total disability score at Visit 2 **(Table 3)**.

Shoulder pain at rest and on movement significantly improved from baseline to the end of treatment in both groups, and further improvement was observed during the follow-up period. Pain decreased more pronounced in the balneotherapy group than in the control group. A significant difference in pain at rest was seen between the two groups at Visits 3 and 4 and in pain on movement at Visit 2 **(Table 3)**.

The role limitations due to physical health, energy/fatigue, and pain domains measured by the SF-36 quality of life questionnaire significantly improved in both groups. This improvement was greater in the balneotherapy group compared to the control group. The difference was not significant. Physical functioning, emotional well being and general health improved significantly in the balneotherapy group only, the difference between the two groups was not significant. The improvement of the role limitations due to emotional problems and social functioning was not significant in any of the groups **(Table 4)**.

The EQ-5D index and VAS general health score of the EuroQol-5D quality of life questionnaire significantly improved in both groups. Improvement was more pronounced in the balneotherapy group. The difference between the two groups was not significant except for EQ-5D index at Visit 2 **(Table 5)**.

Active anteflexion and active retroflexion significantly improved in both groups. Active abduction and active outer rotation improved significantly in the balneotherapy group only. The improvement of the active adduction was not significant in any of the groups. The difference in the active range of motion was not significant between the two groups at any visits **(Table 6)**.

Regarding the passive glenohumeral joint range of motion the improvement was not significant in any of the groups after treatment **(Table 6)**.

Discussion

Our study showed that balneotherapy may have a beneficial effect on the clinical parameters and quality of life of patients with chronic shoulder pain.

Previous reports have demonstrated the beneficial effects of exercise therapy [39-42]. In our study, this benefit is observed in the changes of the control group. According to the results of our study, balneotherapy combined with exercises and TENS provided better results regarding

pain, shoulder function and quality of life than exercises plus TENS, notwithstanding the statistical power of the study was low.

Despite the fact that balneotherapy is a widely used therapeutic method in the treatment of chronic shoulder pain, our study is the first randomized, controlled study, which evaluated the efficacy of mineral water tratment in patients with chronic shoulder pain.

Until now, only one uncontrolled Turkish balneotherapy study has been published about evaluating the effects of hot mud packs on shoulder pain. In this study, Sen U et al. enrolled 29 patients suffering from subacromial impingement syndrome for at least 3 months. Patients received 45°C mud packs on their painful shoulders for 30 minutes once a day for 15 days. A significant improvement in pain was observed during rest, night, and activity as well as in joint function [44].

The treatment of chronic shoulder pain has no been established yet. Evidence exists that exercise decreases pain and improves function in chronic periarticular shoulder pain [39-42]. However, little data is available concerning the effect of electrical therapy [43].

Kromer TO et al. published in 2009 that moderate evidence exists that physiotherapist-led exercises and surgery have similar efficacy in the treatment of impingement syndrome in the long term. These data indicate the importance of conservative therapy before surgery. Home-based exercise program is as effective as combined physiotherapy (exercise: centering training, mobilization; electric therapy) in the short term and long term. Also, there is moderate evidence that manual therapy combined with exercise is superior in pain relief compared to exercise alone. Moderate evidence exists that passive treatments (ultrasound, magnetotherapy, laser) are not effective compared to placebo [41].

Marinko LN et al. metaanalysed on 17 RCTs involving patients with painful shoulder. Exercise had positive effects on pain and function compared to other treatments. However, the change in range of motion were inconclusive [40].

The systematic review of Hanratty CE et al. published in 2012 included 16 RCTs involving 1162 patients. Strong evidence was showen that exercise improved pain and function in subacromial impingement syndrome in the short term. There is moderate evidence that exercise has positive effects on mental status in the short term and improves physical function in the long term. Based on the results of the meta-analysis of 6 studies, the authors concluded that exercise had small positive effect on rotator cuff muscle strength in the short term and small positive effect on long-term function [39].

TENS therapy is widely used in the treatment of rheumatic conditions (e.g. chronic low back pain, osteoarthritis of the knee) and non- rheumatic disorders (e.g. diabetic neuropathy, cancer pain), the efficacy of TENS is still controversial [130].

In a study involving 40 patients with rotator cuff tendinitis, Eyigor C et al. found that although intra-articular steroid decreased pain and improved function more pronounced compared

to TENS therapy especially in the first weeks of treatment, TENS therapy alone was also effective in improving activity, function, and quality of life in the long term [43]. TENS uses analgesic currents, and while its mechanism of action is not complitely understood it is thought that it serves to release endogenous opiates in specific areas of the central nervous system [131].

In our study, water temperature was in the thermoneutral zone, therefore probably the mechanical effects were predominant.

Since no uniform diagnostic and classification criteria exist, we established arbitrary criteria. Based on the inclusion and exclusion criteria, the X-ray and ultrasound examinations made the establishment of relatively homogeneous patient groups. This study is considered to be a pilot study. According to its results, with sample size calculation and determination of the main criteria for a future study, the expansion of the number of the patients would be promising.

Limitation of the study

A single-blind method was used, therefore, the patients knew which treatment they received. Being all questionnaires self-reported, the assessor was the patient and blinding of assessor was not possible, the influence of the placebo effect could be increased. The lack of blinding of therapists, that may overestimate the treatment effect. The procedure evaluating the side effects might be able to underestimate it in both groups. Inspite of the fact that concomittant treatments were not reported, it is difficult to evaluate it. Continuous outcome can lead to a significant placebo effect. Being a small study, the treatment effect might be overestimated. The effect of balneotherapy and hydrotherapy cannot be distinguished in our study. Expansion the number of the patients would be promising.

This chapter was published during my PhD work.
With kind permission from Springer Science+Business Media:
Tefner IK, Kovács Cs, Gaál R, Koroknai A, Horváth R, Badruddin MR, Borbély I, Nagy K, Bender T. The effect of balneotherapy on chronic shoulder pain. A randomized, controlled, single-blind, follow-up trial. A pilot study. Clin Rheumatol 2013 dec 17 [Epub ahead of print]

	Group	Visit 1 (baseline)			Visit 2			Visit 3			Visit 4			p	w
		Mean ±SD	p	Effect size (95% CI)	Mean±SD	p	Effect size (95% CI)	Mean±SD	p	Effect size (95% CI)	Mean±SD	p	Effect size (95% CI)		
VAS pain at rest	Treated (n=23)	32.57±26.47	0.396	0.13 (0.04 to 0.29)	10.04±19.53	0.087	0.25 (0.07 to 0.43)	6.57±16.03	0.007	0.4 (0.21 to 0.57)	6.13± 15.49	0.013	0.36 (0.19 to 0.54)	<0.001	0.606
	Control (n=23)	38.65±24.05			23.26±27.12			23.57±24.71			21.43± 24.52			<0.001	0.304
VAS pain on movement	Treated (n=23)	64.61±22.88	0.150	0.21 (0.04 to 0.39)	34.76±25.50	0.022	0.34 (0.16 to 0.51)	25.33±22.62	0.040	0.3 (0.13 to 0.48)	21.65± 24.02	0.054	0.28 (0.11 to 0.46)	<0.001	0.705
	Control (n=23)	73.00±19.32			51.91±21.61			42.70±30.86			39.39± 32.60			<0.001	0.594
SPADI total pain score	Treated (n=23)	57.74±27.55	0.106	0.24 (0.06 to 0.41)	43.91±27.07	0.129	0.22 (0.05 to 0.4)	36.91±30.73	0.077	0.26 (0.08 to 0.43)	29.39± 28.66	0.039	0.31 (0.13 to 0.48)	<0.001	0.415
	Control (n=23)	70.43±22.46			57.04±25.37			51.46±27.46			50.70± 33,22			<0.001	0.258
SPADI total disability score	Treated (n=23)	47.32±27.16	0.099	0.24 (0.07 to 0.42)	26.53±20.80	0.012	0.37 (0.19 to 0.55)	23.08±23.75	0.043	0.3 (0.12 to 0.48)	23.03± 24.76	0.140	0.22 (0.04 to 0.39)	<0.001	0.4
	Control (n=23)	60.76±26.29			44.40±25.25			40.11±27.67			39.35± 33.30			0.001	0.24
SPADI total score	Treated (n=23)	52.23±27.26	0.127	0.23 (0.05 to 0.4)	33.29±22.72	0.026	0.33 (0.15 to 0.5)	28.40±25.65	0.086	0.25 (0.08 to 0.42)	25.47± 26.60	0.069	0.28 (0.09 to 0.44)	<0.001	0.418
	Control (n=23)	64.38±23.59			49.26±24.56			42.47±28.65			43.71± 32.55			0.003	0.2

Table 3 The VAS pain scores at rest and on movement, the SPADI pain, function, and total scores and their changes in comparison with baseline in the group treated with balneotherapy and in the control group, and the between-group differences in patients with chronic shoulder pain

	Group	Visit 1 (baseline)			Visit 2			Visit 3			Visit 4			p	w
		Mean ±SD	p	Effect size (95% CI)	Mean±SD	p	Effect size (95% CI)	Mean±SD	p	Effect size (95% CI)	Mean±SD	p	Effect size (95% CI)		
Physical functioning	Treated (n=23)	63.48±26.77	0.574	0.08 (-0.09 to 0.26)	73.04±21.57	0.201	0.19 (0.01 to 0.36)	76.09±25.40	0.145	0.22 (0.04 to 0.39)	77.83±25.75	0.153	0.21 (0.04 to 0.39)	<0.001	0.29
	Control (n=23)	60.22±23.91			62.61±26.58			66.52±25.96			69.78±24.42			0.052	0.11
Role limitations due to physical health	Treated (n=23)	34.78±41.11	0.223	0.18 (0.01 to 0.35)	54.35±38.91	0.278	0.16 (-0.02 to 0.33)	60.87±43.83	0.267	0.17 (-0.01 to 0.34)	69.57±38.40	0.068	0.27 (0.09 to 0.45)	<0.001	0.27
	Control (n=23)	21.74±34.79			42.39±46.73			45.65±48.06			45.65±46.25			0.003	0.21
Role limitations due to emotional problems	Treated (n=23)	57.97±41.70	0.457	0.11 (-0.07 to 0.28)	71.01±40.58	0.304	0.15 (-0.02 to 0.33)	76.81±40.74	0.076	0.26 (0.09 to 0.44)	75.36±36.54	0.128	0.22 (0.05 to 0.4)	0.216	0.07
	Control (n=23)	49.28±45.91			59.42±41.38			57.97±44.06			55.07±45.63			0.063	0.11
Energy/ fatigue	Treated (n=23)	49.57±20.16	0.612	0.08 (-0.1 to 0.24)	61.09±17.71	0.067	0.27 (0.09 to 0.45)	63.70±21.44	0.230	0.18 (0.01 to 0.35)	70.22±22.94	0.043	0.3 (0.12 to 0.48)	<0.001	0.3
	Control (n=23)	45.87±27.66			50.00±24.59			54.35±28.05			55.87±25.43			0.003	0.21
Emotional well being	Treated (n=23)	68.00±20.04	0.271	0.16 (-0.01 to 0.34)	75.48±15.32	0.021	0.34 (0.16 to 0.52)	74.78±20.02	0.234	0.18 (0.01 to 0.35)	80.52±20.76	0.061	0.28 (0.1 to 0.45)	0.001	0.23
	Control (n=23)	60.52±24.01			60.70±23.13			66.09±24.68			67.30±24.79			0.015	0.15
Social functioning	Treated (n=23)	66.30±27.55	0.539	0.09 (-0.08 to 0.27)	76.630±25.65	0.308	0.15 (-0.02 to 0.32)	78.26±25.06	0.352	0.14 (-0.04 to 0.31)	83.70±26.23	0.062	0.28 (0.1 to 0.45)	0.012	0.16
	Control (n=23)	72.28±22.60			70.11±26.58			71.20±26.50			71.74±25.34			0.915	0.01
Pain	Treated (n=23)	41.63±24.81	0.417	0.12 (-0.06 to 0.29)	58.37±18.85	0.037	0.31 (0.13 to 0.48)	66.63±24.65	0.053	0.29 (0.11 to 0.46)	72.82±26.19	0.047	0.29 (0.12 to 0.47)	<0.001	0.55
	Control (n=23)	34.02±16.09			45.98±19.51			50.65±24.32			55.76±29.71			0.001	0.23
General health	Treated (n=23)	46.96±15.57	0.146	0.22 (0.05 to 0.4)	53.26±15.05	0.040	0.31 (0.12 to 0.48)	57.39±15.07	0.018	0.35 (0.17 to 0.52)	58.26±16.69	0.014	0.36 (0.18 to 0.54)	0.001	0.24
	Control (n=23)	40.00±26.67			38.26±24.15			41.74±26.18			40.65±27.02			0.835	0.01

Table 4 The SF-36 quality of life questionnaire domains and their changes in comparison with baseline in the group treated with balneotherapy and in the control group, and the between-group differences in patients with chronic shoulder pain

	Group	Visit 1 (baseline)			Visit 2			Visit 3			Visit 4			p	w
		Mean ±SD	p	Effect size (95% CI)	Mean±SD	p	Effect size (95% CI)	Mean±SD	p	Effect size (95% CI)	Mean±SD	p	Effect size (95% CI)		
EQ-5D	Treated (n=23)	0.584±0.183	0.058	0.27 (0.09 to 0.44)	0.755±0.124	0.012	0.37 (0.19 to 0.55)	0.762±0.214	0.071	0.27 (0.09 to 0.44)	0.786±0.202	0.038	0.31 (0.13 to 0.48)	<0.001	0.36
	Control (n=23)	0.455±0.243			0.598±0.217			0.636±0.253			0.650±0.269			<0.001	0.331
EQ VAS	Treated (n=23)	55.65±18.43	0. 860	0.03 (-0.15 to 0.2)	70.00±16.18	0.491	0.1 (-0.07 to 0.28)	74.57±19.34	0.395	0.13 (-0.05 to 0.3)	81.43±15.94	0.066	0.25 (0 08 to 0.43)	<0.001	0.44
	Control (n=23)	52.74±21.98			63.96±19.74			69.57±19.34			68.43±23.63			0.001	0.28

Table 5 The EQ-5D index and VAS general health score of the EuroQol-5D quality of life questionnaire and their changes in comparison with baseline in the group treated with balneotherapy and in the control group, and the between-group differences in patients with chronic shoulder pain

	Group	Visit 1 (baseline)			Visit 2			Visit 3			Visit 4			p	w
		Mean ±SD	p	Effect size (95% CI)	Mean±SD	p	Effect size (95% CI)	Mean±SD	p	Effect size (95% CI)	Mean±SD	p	Effect size (95% CI)		
Active anteflexion	Treated (n=23)	129.26±37.69	0.206	0.18 (0.11 to 0.36)	149.43±28.29	0.103	0.24 (0.06 to 0.42)	152.26±20.32	0.092	0.25 (0.07 to 0.42)	151.87±22.11	0.081	0.26 (0.08 to 0.43)	0.001	0.25
	Control (n=23)	118.04±35.67			139.61±23.73			137.22±31.28			133.39±37.06			0.002	0.22
Active retroflexion	Treated (n=23)	42.78±17.59	0.800	0.04 (-0.14 to 0.21)	50.43±11.86	0.574	0.08 (-0.09 to 0.25)	52.26±15.69	0.230	0.18 (0.01 to 0.35)	49.70±13.52	0.708	0.06 (-0.12 to 0.23)	0.004	0.2
	Control (n=23)	40.13±14.86			48.35±13.75			46.61±14.82			48.04±14.22			0.001	0.24
Active abduction	Treated (n=23)	110.74±35.74	0.416	0.12 (-0.05 to 0.3)	144.17±25.20	0.132	0.22 (0.05 to 0.4)	147.30±27.74	0.074	0.26 (0 09 to 0.44)	140.43±34.21	0.422	0.12 (-0.06 to 0.29)	<0.001	0.33
	Control (n=23)	119.13±36.81			131.91±28.52			130.13±34.63			129.43±40.44			0.070	0.1
Active adduction	Treated (n=23)	22.91±11.01	0.204	0.19 (0.01 to 0.36)	26.91±10.37	0.092	0.25 (0.07 to 0.42)	27.70±12.93	0.408	0.12 (-0.05 to 0.29)	30.22±16.19	0.374	0.01 (-0.16 to 0.18)	0.019	0.14
	Control (n=23)	19.13±10.46			22.00±11.24			23.70±9.99			25.13±12.44			0.039	0.12
Active outer rotation	Treated (n=23)	37.91±19.02	0.991	0.01 (-0.17 to 0.18)	41.96±21.23	0.900	0.02 (-0.16 to 0.19)	49.00±21.92	0.517	0.1 (-0.08 to 0.27)	47.17±18.26	0.232	0.18 (0.01 to 0.35)	0.001	0.23
	Control (n=23)	37.09±19.05			40.86±17.40			43.86±17.60			40.68±20.30			0.712	0.02
Passive anteflexion	Treated (n=23)	82.74±15.88	0.722	0.05 (-0.12 to 0.23)	84.39±13.19	0.686	0.06 (-0.12 to 0.23)	85.91±10.90	0.312	0.15 (-0.03 to 0.32)	85.87±12.06	0.563	0.09 (-0.09 to 0.26)	0.151	0.08
	Control (n=23)	84.39±8.97			84.13±10.73			84.57±9.88			84.35±12.28			0.840	0.01
Passive retroflexion	Treated (n=23)	34.17±19.33	0.659	0.06 (-0.1 to 0.23)	37.57±15.36	0.537	0.09 (-0.08 to 0.27)	38.13±17.24	0.791	0.04 (-0.14 to 0.21)	37.91±15.49	0.868	0.02 (-0.15 to 0.2)	0.243	0.06
	Control (n=23)	34.30±14.21			35.70±14.73			38.13±16.04			38.30±15.56			0.136	0.08
Passive abduction	Treated (n=23)	83.26±11.27	0.525	0.09 (-0.08 to 0.27)	86.26±7.65	0.269	0.16 (-0.01 to 0.34)	88.39±9.56	0.039	0.31 (0.13 to 0.48)	87.39±6.19	0.026	0.33 (0.15 to 0.51)	0.037	0.12
	Control (n=23)	82.17±11.95			82.70±10.73			82.17±9.91			81.61±11.13			0.448	0.04
Passive outer rotation	Treated (n=23)	68.43±28.72	0.735	0.05 (-0.12 to 0.22)	80.30±21.28	0.239	0.17 (-0.01 to 0.35)	80.39±22.11	0.369	0.13 (-0.04 to 0.31)	82.70±17.19	0.078	0.26 (0.08 to 0.44)	0.011	0.16
	Control (n=23)	69.87±23.20			77.09±20.65			78.26±18.80			75.26±23.49			0.297	0.05
Passive inner rotation	Treated (n=23)	33.04±19.03	0.598	0.08 (-0.1 to 0.25)	39.43±18.36	0.027	0.32 (0.14 to 0.5)	34.91±17.07	0.877	0.02 (-0.15 to 0.19)	38.43±15.80	0.064	0.27 (0.1 to 0.45)	0.023	0.14
	Control (n=23)	30.52±18.46			27.96±15.75			32.72±16.71			29.04±16.39			0.533	0.03

Table 6 The active shoulder girdle range of motion and the passive glenohumeral joint range of motion and their changes in comparison with baseline in the group treated with balneotherapy and in the control group, and the between-group differences in patients with chronic shoulder pain

THE EFFECT OF NEYDHARTING MUD PACK THERAPY ON KNEE OSTEOARTHRITIS. A RANDOMIZED, CONTROLLED, DOUBLE-BLIND FOLLOW-UP PILOT STUDY

Objectives

The controlled clinical studies evaluating the effects of peloid therapy in osteoarthritis of the knee were detailed in the Literary overview [67-73]. These studies showed the effect of mud pack therapy compared to the control group, but according to our opinion, they never fulfilled the double-blind conditions and the appropriate controllability at the same time. Therefore the primary endpoint of our study was to investigate whether Neydharting mud pack had a similar positive effect on the clinical parameters in patients with knee osteoarthritis, and how large this effect was compared to that of an artificially produced control pack in a double-blind trial with adequate controllability. The secondary endpoint was to evaluate the effect of clinical improvement on the quality of life and need for medications in the mud-treated group compared to the control group.

Protocol and study parameters

Design

This was a randomized (1:1), double blind controlled parallel-group prospective study investigating the effect of Neydharting mud pack therapy on knee osteoarthritis. The study was carried out at the Department of Rheumatology and Physiotherapy of the Józsefváros Health Care Services, Budapest (Hungary).

Participants

Patients with the following conditions were enrolled to the study: outpatients with slightly reduced mobility, suffering from chronic knee pain; knee osteoarthritis according to American College of Rheumatology (ACR) criteria [132]; women and men aged 40-75 years; symptoms have been present for at least 3 months; at least mild knee pain on exertion (Likert scale: 1 point); Kellgren-Lawrence radiological grade 1-3.

Exclusion criteria were: medical history of surgery on the affected knee joint (arthroscopy is allowed); arthroscopy of the affected knee joint within 6 months prior to treatment; hip joint or spinal surgery within 6 months prior to treatment; current knee pain is caused by obvious trauma; systemic or local steroid therapy or balneotherapy within 2 months prior to treatment; TENS therapy is allowed up to two weeks prior to treatment; physiotherapy is allowed; intra-articular hyaluronic acid therapy within 12 months prior to treatment; starting

new oral Symptomatic Slow Acting Drugs in Osteoarthritis (SYSADOA) therapy within 3 months prior to treatment; lumbar radiculitis; palpable and significantly tender Baker's cyst; synovitis; inflammatory joint disorder; flexion contracture (greater than 10 degrees); general contraindications of balneotherapy.

Study participants were patients under regular care recruited according to the study protocol by the rheumatologists of the Józsefváros Health Care Service, Budapest (Hungary). This study was conducted between August and November of 2012. Treatment took place between 6 and 17 August 2012 on 10 working days at the Department of Rheumatology and Physiotherapy of the Józsefváros Health Care Services in rooms adapted for this purpose. Study participants received written information and they signed an informed consent form before the study. The study has been approved by the regional ethics committee (24/2012).

Intervention

One group of patients received Neydharting mud pack and the other group received control hot pack on a total of 10 occasions, for 30 minutes per occasion, 5 times a week for 2 weeks. The temperature of the packs was 42ºC in both groups.

The study was performed by using Neydharting mud. Neydharting valley is located in Upper Austria. The Neydharting moor mud has been traditionally used in packs and baths for the treatment of musculoskeletal disorders. The Neydharting mud is a lowland moor turf mud considered as sedimentary peloid. The original sample is a week acid (pH: 6.4) with 83.2% water and 16.77% dry weight, of which 12.05% is loss of ignition (indicating organic material content). 32.56% of the organic material is humic acid (which is considered high). Inorganic material content is also relatively high (4.72%) [133].

The control group received treatment with a substance having similar physical properties (viscosity, plasticity, adherence to skin, water-binding capacity, and color) to that of the Neydharting mud. This substance was produced specifically for the study under pharmacy conditions. It was made of suitable proportions of commonly used pharmaceutical materials deemed to be the simplest and most necessary. Our aim was to prevent the patients from discovering which treatment (mud or artificially produced pack) they receive **(Photo 2)**. The control pack (1000 g) contained zinc oxide (45 g), talc (45 g), glycerol 85% (250 g), activated carbon (285 g), and purified (distilled) water (375 g).

Patients completing more than 80% of the treatments were considered completing the study.

Outcomes

Completion of disease-specific questionnaires (WOMAC Likert scaled version) [115-116] as primary outcome and completion of quality of life (EuroQoL-5D) questionnaires as secondary outcome were performed before the first treatment (at Week 0), after Treatment 10 (at Week

2), as well as 3 and 10 weeks after Treatment 10 (at Weeks 6 and 12, respectively). As further secondary outcome, the daily and weekly doses of analgesics and NSAIDs for knee pain were recorded 1 month before treatment, during the treatment, and in the follow-up period. A health survey including a detailed past medical history, verification of inclusion and exclusion criteria, recording of possible side effects and physical examination was also performed.

Randomization, and blinding

The person randomizing the patients received patient information via e-mail and used a computer program for the randomization. After randomization, an independent person assigned the patients into the appropriate groups (assigned treatment number to patient ordinal number). The study staff applied treatment from the numbered jars on the affected knee. The patients did not know which treatment they received and they also did not discover it during treatment, since treatment was performed in treatment rooms separated by curtains. An independent assessor blinded to the treatment examined the patients before treatment, at the end of treatment, and during the follow-up visits. The independent blinded physician supervising the treatment was available during the treatments and he was the one to detect possible side effects. The professional performing the statistical analysis was independent.

Statistical analysis

Statistical analysis was performed by using IBM SPSS Statistics 20. Nonparametric methods were used in statistical calculations, due to the sample size. Data obtained from WOMAC, from EQ-5D questionnaires and from the need for medication (the mean number of tablets per week) were analyzed by Mann-Whitney test and Friedman's test. Significance value was 0.05. The number of patients requiring analgesics and NSAIDs were compared by McNemar's test. Significance value was 0.017 with Bonferroni correction. The WOMAC Likert indices were normalized on 0-100 scales. The results were evaluated by intention-to-treat analysis.

Results

Fifty-three patients were randomized, 27 received mud therapy and 26 were assigned to the control group. During treatment, two patients refused treatment in the mud-treated group (one of them due to increasing knee pain and the other is for personal reasons) and two patients stopped treatment in the control group (one patient due to thrombophlebitis and the other patient for personal reasons). The rest of the patients participated in at least 80% of the treatment. During the follow-up period, one patient in the control group required intra-articular and oral steroid therapy for knee joint synovitis after Visit 2 and thus was excluded from the study. Due issues with compliance, one patient in the control group did not come to Visit 4. No other side effects were

detected during the study or the follow-up period. According to the intention-to-treat analysis, all patient data had been processed.

At the beginning of the study, the demographic and measured parameters of the two groups were comparable. Eight patients were male and 45 patients were female (mean age 63.42±8.86 and 63,55±9.53 years, respectively).

The WOMAC pain, stiffness, function, and total scores, the EQ5D quality of life score, and the VAS score indicating the current health condition improved from baseline to the end of treatment in both groups, and further improvement was observed during the follow-up period. Although there were no significant differences between the two groups in any of the parameters at any visits, clinical improvement was consistently greater in the mud-treated group compared to controls **(Table 7)**, **(Fig. 1 and Fig. 2)**.

The need of analgesics and NSAIDs (mean number of tablets per week) for knee pain improved significantly only in the mud treated group compared to baseline. In the control group, the changes were not significant. The differences between the two groups were not significant at any visits **(Table 7)**.

The number of patients requiring analgesics and NSAIDs showed a continuous downward trend at the subsequent post-treatment visits in the mud-treated group, and these changes became significant by Visit 4 compared to baseline. The control group showed only temporary decrease and the changes were not significant. The differences between the two groups were not significant at any visits **(Table 8)**.

Discussion

Our results show that Neydharting mud hot pack has a definite positive effect on the clinical parameters (pain and joint stiffness decreased and joint function improved), quality of life, and need for medications in patients with knee osteoarthritis, and this was observed even during the follow-up period. The favorable changes observed in the control group can be explained by the heat effect per se, but in our opinion, the physical properties of the control material resulting from its composition and fine granular structure similar to that of the mud (water-binding capacity, heat storage capacity, adhesive properties, adherence to skin, etc.) also contributed to its positive effects.

Talc in the control material belongs to clay minerals. Clay-water mixture is traditionally used in therapy in the form of a pack (geotherapy) [6]. As yet, there are no data about the comparison of geotherapy and mud/peloid therapy in the clinical setting.

In our opinion most of the effect might be due to heat, and the clear trend showed between the groups and some significant, positive changes (decrease in need for medications) observed only in the mud-treated group in our study might indicate an additional specific chemical effect

of the mud. In our opinion it could be the relatively low patient number which made the differences between the two groups non-significant; however, a consistent trend was seen. Based on the clear improvement and the fact that the difference between the two groups seen on the graphics as well shows a trend, it would be promising to increase the number of patients in the future.

Clinical trials on the effect of mud therapy suggested its effectiveness on osteoarthritis of the knee [67-73], and some of them showed that it is more effective than the control treatment [67-68, 72]. Reviewing these trials we can conclude that our study is the first investigation regarding the effect of mud pack therapy fulfilling double-blind conditions as well as appropriate controllability (not home treatment but outpatient treatment under standard circumstances and with the help of a qualified medical staff). In the above mentioned controlled studies, there was at least a bigger chance that the patient discovered which treatment he/she received (control pack for home use [67, 71], or the treatment was not kept as a secret (nylon-covered mud pack [68], hot pack without patient blindness [70, 72-73], or intraarticular hyaluronic acid treatment [69]). Under our strict study conditions, placebo effect probably prevailed in both groups. Apart from relatively low patient number, this may also explain why there is less difference in improvement between the two groups in our study than in the above mentioned studies. In our opinion, the changes in need for medications objectively and indirectly reflect the changes in the patients' condition. In our study, need for medication decreased significantly and long-term only in the mud-treated group, whereas the control group showed only a temporary trend. In the study of Odabasi et al., need for medications in the groups changed similarly as in our study [68]. It is noteworthy, that although the patients received outpatient treatment and otherwise lived a normal lifestyle, so the effect of climate and bathing area could be omitted.

The number and length of treatments were higher in most of the previous studies. There is no consensus or evidence in this regard; since our patients received outpatient treatment, we decided to use the above treatment parameters primarily due to the control group.

Limitation of the study

The study is not powered enough to make any conclusion about the differences between the groups. It would be promising to increase the number of patients in the future.

This chapter was published during my PhD work.
With kind permission from Springer Science+Business Media:
Tefner IK, Gaal R, Koroknai A, Ráthonyi A, Gáti T, Monduk P, Kiss E, Kovács C, Bálint G, Bender T. The effect of Neydharting mud-pack therapy on knee osteoarthritis: a randomized, controlled, double-blind follow-up pilot study. Rheumatol Int 2013; 33:2569-76.
Figure 2 and 3.

	Group	Visit 1 (baseline)		Visit 2 (week 2)		Visit 3 (week 6)		Visit 4 (week 12)		Significance level (differences among visits)
		Mean±SD	Significance level (between- group difference)	Mean±SD	Significance level (between- group difference)	Mean±SD	Significance level (between- group difference)	Mean±SD	Significance level (between- group difference)	
WOMAC pain score	Mud hot pack (n=27)	50.20±14.51	0.231	28.80±17.78	0.879	24.07±18.45	0.623	23.33±19.16	0.598	<0.001
	Control (n=26)	45.60±20.07		30.00±20.25		28.65±21.84		26.54±19.64		<0.001
WOMAC stiffness score	Mud hot pack (n=27)	55.56±18.12	1.000	33.80±25.43	0.267	36.11±22.29	0.878	32.87±23.29	0.685	<0.001
	Control (n=26)	54.81±22.10		40.40±20.71		38.46±24.73		36.05±25.33		<0.001
WOMAC function score	Mud hot pack (n=27)	51.34±16.84	0.824	34.83±22.73	0.471	31.48±22.61	0.533	28.35±23.58	0.359	<0.001
	Control (n=26)	50.54±19.38		34.00±21.32		36.75±22.61		33.58±21.45		<0.001
WOMAC total score	Mud hot pack (n=27)	51.38±15.27	0.669	33.44±20.98	0.488	30.29±20.99	0.476	27.64±22.07	0.408	<0.001
	Control (n=26)	49.80±18.53		37.19±20.03		35.16±21.75		32.28±20.52		<0.001
EQ-5D index	Mud hot pack (n=27)	0.49±0.220	0.325	0.63±0.252	0.780	0.70±0.267	0.244	0.72±0.247	0.250	<0.001
	Control (n=26)	0.56±0.170		0.63±0.196		0.63±0.200		0.66±0.161		<0.001
VAS score of overall health status (mm)	Mud hot pack (n=27)	59.33±21.485	0.361	70.44±21,389	0.290	73.63±21.408	0.218	72.44±23.159	0.335	<0.001
	Control (n=26)	53.77±16.437		66.00±17.069		67.38±20.290		67.62±19.948		<0.001
Analgesics and NSAID requirement, tablets/week	Mud hot pack (n=27)	2.81±4.756	0.985	1.88±4.098	0.814	1.35±3.889	0.242	1.33±3.893	0.099	<0.001
	Control (n=26)	1.79±3.245		1.58±3.349		1.28±3.047		1.30±3.046		0.106

Table 7 Study parameters and their changes in comparison with baseline after mud hot pack therapy and the control hot pack therapy, and the between-group differences in patients with OA of the knee

	Group	Visit 1 (baseline)		Visit 2 (week 2)		Visit 3 (week 6)		Visit 4 (week 12)	
		Number of patients	Significance level (between- group difference)	Number of patients	Significance level (between- group difference)	Number of patients	Significance level (between- group difference)	Number of patients	Significance level (between- group difference)
Analgesics and NSAID requirement	Mud hot pack (n=27)	10	NS	7 NS	NS	5 NS	NS	3 P=0.016	NS
	Control (n=26)	8		6 NS		6 NS		8 NS	

Table 8 Study parameters and their changes in comparison with baseline after the mud hot pack therapy and the control hot pack therapy, and the between-group differences in patients with OA of the knee

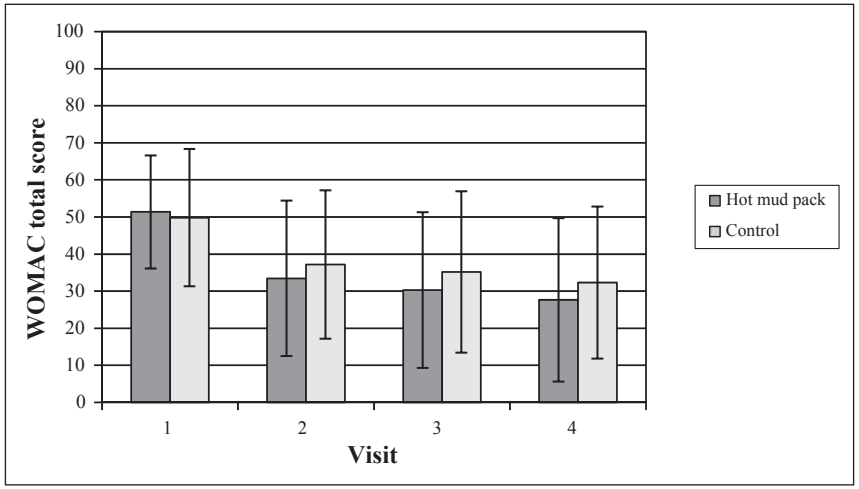

Figure 1 The WOMAC total score and its changes after mud hot pack and control hot pack therapy

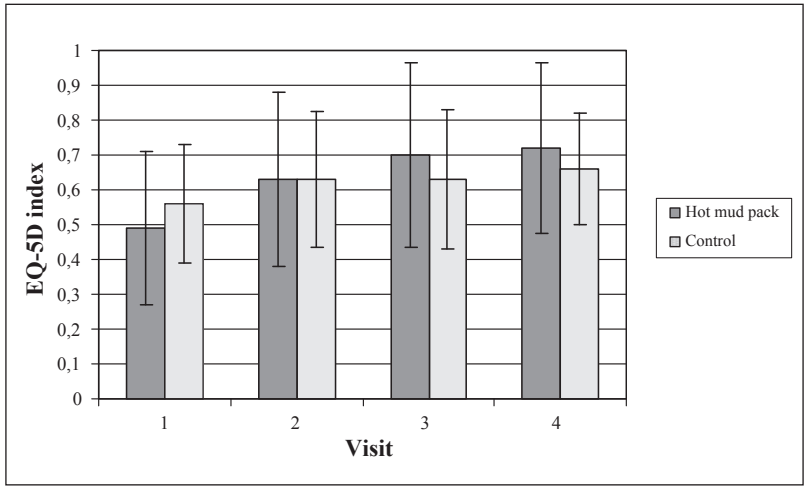

Figure 2 EQ-5D index and its changes after mud hot pack and control hot pack therapy

THE EFFECTS OF KOLOP PELOID ON KNEE OSTEOARTHRITIS IN DAY HOSPITAL CARE. A RANDOMIZED, CONTROLLED, SINGLE-BLIND, FOLLOW-UP PILOT STUDY

Objectives

Combined physiotherapy is a therapeutic method with cumulative effects when a physiotherapy plan is made taking into account the patient's condition, disease activity, and the aims to be achieved. In Hungary, combined spa treatment or as its former and internationally accepted name, day hospital care for musculoskeletal disorders is of great importance from the professional standpoint. One of the basic profiles of the day care hospitals in Budapest is peloid therapy. The day care hospitals in Budapest use Kolop peloid for this purpose. In peloid therapy, the thermophysical properties of Kolop peloid predominate, and when the peloid is used mixed with the thermal mineral waters of Budapest, it is considered as "complete" [134].

To date, no studies have been published in the English literature evaluating the effects of peloid therapy as part of combined physio- and balneotherapy treatment, evaluating the effect of peloid pack therapy plus standardized, combined physiotherapy and balneotherapy treatment versus combined physiotherapy and balneotherapy treatment without peloid pack therapy.

The primary objective of our study was to evaluate the beneficial effect of Kolop peloid on the clinical parameters of patients with knee osteoarthritis in the day hospital care setting, and how strong this effect was compared to the control group. Our secondary objective was to find out the effect of clinical improvement on quality of life compared to baseline and to the control group.

Protocol and study parameters

Design

In this randomized, controlled, follow-up study, we evaluated the effects of Kolop peloid on knee osteoarthritis in patients randomized (1:1) into two groups. The study was performed in the day care hospitals of the Széchenyi and St. Lukács Thermal Baths of the Budapest Bath cPlc.

Participants

Inclusion criteria: patients suffering from chronic knee pain treated in the day care hospitals of the Széchenyi and St. Lukács Thermal Baths of the Budapest Baths cPlc.; diagnosis of knee osteoarthritis based on the ACR criteria [132]; complaints present for at least 3 months; radiologic stage: Kellgren-Lawrence 1-3.

Exclusion criteria were: medical history of surgery on the affected knee joint (arthroscopy is allowed); arthroscopy of the affected knee joint within 6 months prior to treatment;

hip joint or spinal surgery within 6 months prior to treatment; current knee pain is caused by obvious trauma; systemic or local steroid therapy or balneotherapy within 2 months prior to treatment; intra-articular hyaluronic acid therapy within 12 months prior to treatment; starting new oral SYSADOA therapy within 3 months prior to treatment; lumbar radiculitis; palpable and significantly tender Baker's cyst; synovitis; inflammatory joint disorder; flexion contracture (greater than 10 degrees); general contraindications of balneotherapy; TENS therapy was allowed up to two weeks prior to treatment; exercise was allowed.

Study participants were recruited form the day care hospitals of the Széchenyi and St. Lukács Thermal Baths of the Budapest Baths cPlc. by the rheumatologists working in these institutions. The study took place between September 2012 and January 2013. Study participants received written information and signed an informed consent form before the study. The study was approved by the regional ethics committee (approval number: 20822-1/2012).

Intervention

Both groups received standardized, combined physiotherapy and balneotherapy on the painful knee joint for 3 weeks, five days a week, including the following treatments: pool bath in 31°C mineral water for 30 minutes, aquatic exercise in 31°C mineral water for 20 minutes, and magnetotherapy for 15 minutes. In addition, the peloid-treated group received Kolop peloid packs on the painful knee joint for 30 minutes at each session; the temperature of the pack was 42°C. The control group received standardized combined physiotherapy and balneotherapy on the knee joint without peloid packs.

We used Kolop peloid in our study. Kolop is located in Jász-Nagykun-Szolnok county (Hungary) under the municipality of Tiszasüly. It used to be a health resort (Kolop Bath). Kolop peloid has been used in the spas of Budapest since 1920 [135]. Kolop peloid is a river mud mainly consisting of inorganic substances [136].

Outcomes

The WOMAC disease-specific questionnaire [115-116] and the EuroQol-5D quality of life questionnaires were administered before the first treatment (Week 0), after the 3-week treatment (Week 3), and three months after treatment (Week 15).

Randomization, and blinding

The person randomizing the patients used a computer program for randomization. After randomization, an independent person assigned the patients into the appropriate group. Three independent assessors blinded to the treatment examined the patients in a previously standardized manner before treatment, at the end of treatment, and at the follow-up visit. The independent

physicians supervising the treatment were available during the treatments and he/she was the one to detect side effects. Statistical analysis was performed by an independent person.

Statistical analysis

Statistical analysis was performed by using IBM SPSS Statistics 20. Distribution was assessed by the Kolmogorov-Smirnov test. Data obtained from WOMAC and EQ-5D questionnaires were analyzed by independent samples t-test and paired samples t-test. Significance value was 0.05. At multiple comparisons (paired samples t-test), p-value was 0.017 with Bonferroni correction. The WOMAC Likert indices were normalized on 0-100 scales. The results were evaluated by intention-to-treat analysis.

Results

Results obtained from 60 patients were evaluated: 30 patients were treated in the Kolop peloid group and 30 patients in the control group. No side effects were noted. Patient compliance was adequate, all patients attended all visits.

The two groups were comparable in gender (7 men and 23 women participated in the peloid-treated group, and 9 men and 21 women participated in the control group), age, and need for analgesics and NSAIDs (8 patients in the peloid-treated group and 9 patients in the control group received medication for knee pain).

The WOMAC pain, stiffness, function, and total scores significantly improved from baseline to the end of treatment in both groups, and further improvement was observed during the follow-up period **(Table 9)**.

The initial parameters (Week 0) suggested a more severe disease in the peloid-treated group compared to the control group (a significant difference was seen in the WOMAC pain, function, and total scores between the two groups).

However, improvement from baseline to the end of treatment (Week 3) and to the end of the follow-up period (Week 12) was more significant in the Kolop peloid-treated group compared to the control group **(Table 10)**.

The EuroQol-5D quality of life index improved from baseline to the end of treatment in both groups, but this improvement was significant in the control group only; however, at Week 3, there was no significant difference between the two groups. By the end of the follow-up period (Week 12), both groups improved significantly compared to baseline. At the end of the follow-up period (Week 12), the EuroQol-5D quality of life index was significantly better in the Kolop peloid-treated group compared to the control group **(Table 9)**.

The VAS score indicating the current general health status of the patients significantly improved from baseline to the end of treatment in both groups, and further improvement was ob-

served during the follow-up period. At the end of the follow-up period (Week 12), general health status was significantly better in the Kolop peloid-treated group compared to the control group **(Table 9)**.

Discussion

Our study showed the beneficial effects of Kolop peloid on knee osteoarthritis in the short and long term.

According to the results of our study, peloid therapy combined with mineral water bathing, aquatic exercise and magnetotherapy provided significantly better results regarding pain, function and quality of life than mineral water bathing, aquatic exercise and magnetotherapy without peloid therapy.

In our opinion, the reason why patients in the Kolop peloid-treated group had more severe disease at baseline according to the WOMAC score was that several patients with severe disease refused to participate in the study after randomization and before filling the questionnaires, if they did not have the opportunity to receive peloid treatment. These patients were excluded from the study. This difference was indicated less sensitively by the EuroQol-5D questionnaire.

Our study is the first evaluating the additive beneficial effects of mud therapy as part of combined treatment. The randomized, multicenter trial involving 382 patients with knee osteoarthritis by Forestier et al. was detailed in the Literary overview [60].

The improvement observed in the control group is not surprising. The analgesic and function-improving effect of mineral water bathing in patients with knee osteoarthritis has been showen and detailed in the Literary overview [54-58].

It has been shown that land based exercise reduces pain and improves function in patients with osteoarthritis of the knee compared to the group of patients who do not exercise [137]. The Japanese review published in 2010 mentioned in the Literary overview evaluated meta-analyses performed between 1990 and August of 2008 on hydrotherapy, and concluded that aquatic exercise has similar effects to that of land based exercise [47]. According to some recently published, randomized, controlled studies aquatic exercise has a more pronounced analgesic effect in hip and knee osteoarthritis compared to land based exercise [138-139]. Although magnetotherapy is widely used in practice, its effect has not yet been proven [140].

Limitation of the study

Lack of group homogeneity regarding the baseline WOMAC scores. Single-blind method.

This chapter was published during my PhD work.
Horváth R, Domoki M, Tóth É, Bender T, Tefner IK. The effects of Kolop peloid on knee osteoarthritis in day hospital care: a randomised, controlled, single-blind, follow up pilot study. Press Therm Climat 2013; 150:13-23.

	Visit 1 (baseline)			Visit 2 (week 3)			Visit 3 (week 15)		
	Peloid hot pack n=30	control n=30	between-group difference	Peloid hot pack n=30	control n=30	between-group difference	Peloid hot pack n=30	control n=30	between-group difference
	mean (SD)	mean (SD)		mean (SD) nature of change	mean (SD) nature of change		mean (SD) nature of change	mean (SD) nature of change	
WOMAC pain score	47.11 (15.049)	29.47 (14.17)	p<0.001	34.94 (14.042) p<0.001	23.53 (13.265) p<0.001	p=0.002	29.19 (14.339) p<0.001	20.56 (11.298) p<0.001	p=0.012
WOMAC stiffness score	54.45 (19.847)	42.57 (22.525)	NS	39.45 (18.853) p<0.001	33.9 (19.446) p<0.001	NS	31.58 (18.169) p<0.001	30.08 (17.392) p<0.001	NS
WOMAC function score	53.55 (14.93)	39.9 (15.507)	p=0.001	41.69 (14.672) p<0.001	33.82 (15.925) p<0.001	NS	35.49 (15.729) p<0.001	29.23 (13.189) p<0.001	NS
WOMAC total score	155.11 (44.645)	111.94 (48.61)	p=0.001	116.08 (43.224) p<0.001	91.24 (45.372) p<0.001	NS	96.26 (43.64) p<0.001	79.87 (38.46) p<0.001	NS
EQ-5D index	0.61 (0.144)	0.57 (0.184)	NS	0.67 (0.171) NS	0.63 (0.194) p<0.001	NS	0.81 (0.149) p<0.001	0.71 (0.204) p<0.001	p=0.025
VAS score of general health status	52.53 (11.611)	56 (13.386)	NS	63.9 (13.725) p<0.001	61.07 (12.616) p<0.001	NS	71.77 (10.365) p<0.001	64.67 (13.586) p<0.001	p=0.027

Table 9 Study parameters and their changes in comparison with baseline after peloid hot pack therapy and in the control group in patients with OA of the knee, and the between group differences

	Change between visit 2 and visit 1			Change between visit 3 and visit 1		
	Peloid hot pack n=30	Control n=30	Between-group difference	Peloid hot pack n=30	Control n=30	Between-group difference
	mean (SD) nature of change	mean (SD) nature of change		mean (SD) nature of change	mean (SD) nature of change	
WOMAC pain score	12.17 (6.52)	5.94 (6.98)	p=0.001	17.93 (12.12)	8.91 (7.67)	p=0.001
WOMAC stiffness score	15 (7.69)	8.67 (9.9)	p=0.08	22.87 (11.43)	12.48 (12.06)	p=0.001
WOMAC function score	11.85 (5.23)	6.08 (6.47)	p=0.00	18.057 (80.08)	10.67 (8.69)	p=0.01
WOMAC total score	39.03 (17.26)	2.7 (21.82)	p=0.001	58.85 (26.88)	32.07 (27.28)	p=0.00

Table 10 The change of WOMAC pain, stiffness, function and total scores after the peloid hot pack therapy and the control treatment, and the between group differences

EVIDENCE BASED HYDRO- AND BALNEOTHERAPY IN HUNGARY. A SYSTEMATIC REVIEW AND METAANALYSIS

Objectives

Recently, Karagülle and Karagülle [141], as well as Katz et al [142] reviewed the Turkish and Israeli balneological trials, so to follow suit, we decided to undertake a systematic review of the trials by Hungarian authors [141-142]. Our aim was to provide an overview of Hungarian research into the field of balneotherapy. Further, we intended to conduct a meta-analysis of the studies meeting the predefined criteria. We chose the relief of pain as the primary outcome measure, whereas secondary outcome parameters included the improvement of function, activity level, quality of life, the changes of laboratory parameters, and the reduction of analgesic and NSAID requirements.

Methods

Two authors independently screened the Cochrane Library, as well as the PubMed, Web of Science, Scopus, PED-ro, Web of Knowledge databases. The review was limited to studies of Hungarian mineral waters, published by Hungarian authors in the English-language literature between 1989 and 2012. We searched the above-mentioned literature databases using the following search terms: balneotherapy, spa therapy, thermal water, mineral water, radon bath, radon cave, peloid, underwater traction therapy, hydrotherapy. We identified all articles discussing hydro- and balneotherapy in Hungary including reports of clinical, experimental, historical, or semantic studies, as well as letters on the effect of mineral water, radon baths, or cave and peloid treatment. Two reviewers selected clinical trials and extracted their data (study characteristics and results) independently of each other, according to a standard set of criteria. All clinical trials were included in the systematic review. Studies meeting the following criteria were selected for meta-analysis: any form of balneotherapy administered with or without any other treatment; randomized controlled trials; full papers reporting Hungarian studies in English; trials carried out in Hungary; studies with at least one symptom-specific outcome measure, such as pain, function, quality of life, or laboratory findings. The internal validity of the clinical studies was assessed using the 11-point van Tulder scale [143-144]. The authors were contacted and the missing data obtained through personal communication.

Statistical methods

Mean values and standard deviations (SD), or test statistics were recorded for each of the trials selected for metaanalysis, and effect sizes were computed using the standardized mean difference (SMD) technique. The effect sizes were processed with the MedCalc software package.

Results

The literature search identified 122 studies. Among these, we found 18 clinical trials for systematic review [54-55, 58-59, 105-106, 145-156]. Data from 1199 subjects (patients and controls) of the 18 clinical studies were evaluated.

Nine of the 18 clinical trials were excluded. Two studies lacked a proper control group [152, 155]; one study measured the effect of underwater traction and not that of balneotherapy [149]. One additional study evaluated radon cave therapy and not balneotherapy [148]. Following a more detailed review of these provisionally selected articles, further 5 papers were excluded for the following reasons: one study lacked a relevant common endpoint [54], and diverse outcome measures were assessed in at least 4 studies [147, 150-151, 154]. Only studies with a symptom-specific outcome measure evaluated in at least 4 studies were selected. In the end, 9 studies fulfilled the inclusion criteria for meta-analysis [55, 58-59, 105-106, 145-146, 153, 156]. In view of the inclusion criteria, "pain at rest" and "pain on weight bearing" (both measured by VAS) were assessed in 4, and in 9 trials, respectively. If the paper did not specify what kind of pain was measured, we contacted the authors for clarification. We found that "pain on loading" improved significantly in 7 out of the 9 studies **(Fig. 3)**. In this meta-analysis, the overall improvement of "pain on weight bearing" was about 70-80% (SMD – 0,747, 95% CI – 0,931 to – 0,563, fixed effect; SMD – 0,783, 95% CI – 1,144 to 0,422, random effect). "Pain at rest" improved in three out of four studies **(Fig. 4.)**; overall improvement was about 70% (SMD 0,715, 95% CI – 0,998 to 0,433, random effect, SMD – 0,715, 95% CI – 0,998 to 0,433 fixed affect). Using summarized analysis, the aggregate improvement of "pain on weight bearing" and of „pain at rest" was significant. The heterogeneity test was significant for "pain on weight bearing". In 7 trials, "pain on weight bearing" improved significantly relative to the control group treated with heated tap water [55, 58-59, 145-146, 153, 156]. However, in the remaining two trials, the improvement of "pain on weight bearing" was significant also in the tap water group [62-63]. This finding may be explained by the cumulative soothing effect of warm water and concomitant interventions (such as electrotherapy). In these two studies, additional parameters, namely muscle spasm (measured by a manual method) and quality of life improved significantly in patients treated with thermal mineral water, as compared with the controls.

Limitation of the study

The only common feature of the analyzed studies was their primary outcome measure; between-study heterogeneity and methodological flaws prevented the analysis of their secondary endpoints. Occasionally, the type of pain (i.e. pain at rest, at loading or on weight bearing) was ascertained by personal communication with the authors, and not from the information present-

ed in the results section of the papers. The included studies had small patient populations. The studies were most part diverse in terms of the type, intensity, and duration of treatments, as well as in regard of the methodology and timing of clinical assessments.

This chapter was published during my PhD work.
With kind permission from Springer Science+Business Media:
Bender T, Bálint G, Prohászka Z, Géher P, Tefner IK. Evidence-based hydro- and balneotherapy in Hungary-a systematic review and meta-analysis. Int J Biometeorol 2013 May 16. [Epub ahead of print]
Figure 2 and 3

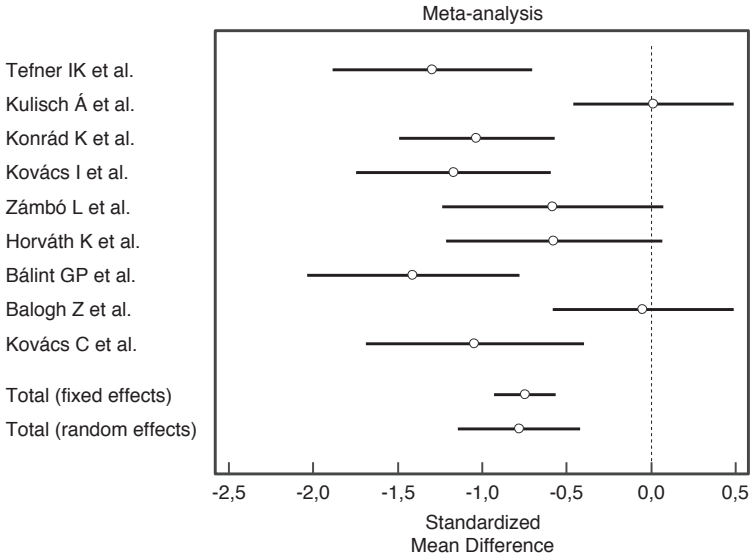

Figure 3 The intensity of pain on loading on visual analogue scale (VAS).
The effect of balneotherapy on pain on loading in the RCTs reviewed

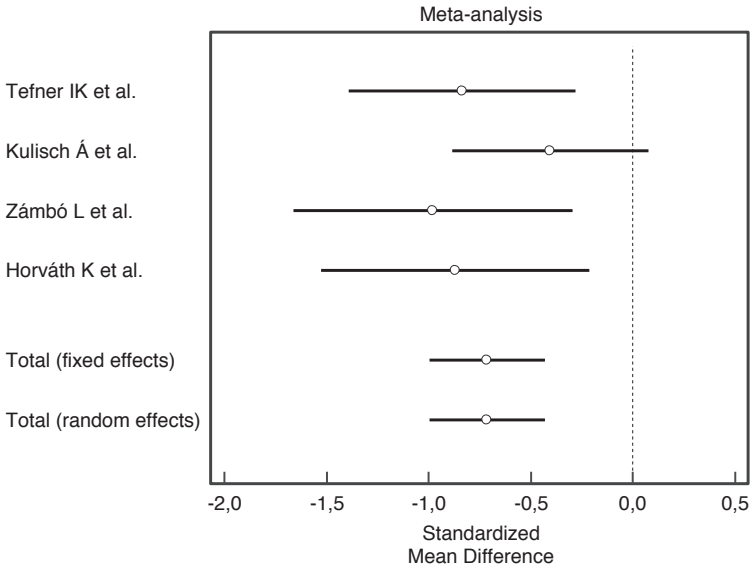

Figure 4 The intensity of pain at rest on visual analogue scale (VAS).
The effect of balneotherapy on pain at rest in the RCTs reviewed

CONCLUSIONS, NEW RESULTS

I./1. Our randomized, controlled, single-blind, follow-up pilot study demonstrated the beneficial effect of immersion in high-mineral-content water from Mátraderecske on clinical parameters (pain reduced, function improved), quality of life and analgesic and NSAID requirements in patients with chronic low back pain, in comparison to immersion in tap water with the same temperature. Balneotherapy may be a possible therapeutic option in the treatment of chronic low back pain.

I./2. Our randomized, controlled, single-blind, follow-up pilot study is the first trial in the English literature evaluating the effect of immersion in mineral water in chronic shoulder pain. Immersion in mineral water combined with exercise and TENS therapy may provide significantly better results than exercise and TENS alone on the clinical parameters of patients suffering from chronic shoulder pain with a possible improvement in the quality of life of patients as well. Based on our results, we can conclude that balneotherapy may be a possible therapeutic option in the treatment of chronic shoulder pain. The number of patients should be increased.

II./1. According to our randomized, controlled, double-blind, follow-up pilot study, we have shown that when used in a hot pack, the Neydharting mud has a strong positive effect on the clinical parameters of patients with knee osteoarthritis, and it also caused a clear improvement in quality of life and a decreased need for medications. The contol materia was produced specifically for the study under pharmacy conditions to prevent the patients from discovering which treatment (mud or artificially produced pack) they receive. By using this materia our study is the first investigation regarding the effect of mud pack therapy fulfilling double-blind conditions as well as appropriate controllability. Our results suggest that most of the effect of hot mud pack therapy might be due to heat. The clear trend showed between the groups and some significant, positive changes observed only in the mud-treated group in our study might indicate an additional specific chemical effect of the mud. To evaluate the chemical effect by increasing the number of patients, would be promising. Based on our results, we can conclude that the Neydharting mud hot pack is a possible therapeutic option in the treatment of knee osteoarthritis.

II./2. According to our randomized, controlled, single-blind follow-up study in the day hospital care setting showed that Kolop peloid has favorable effect on knee osteoarthritis both in the short and long term. Peloid therapy combined with mineral water bathing, aquatic exercise and magnetotherapy provided significantly better results regarding pain, function

and quality of life than mineral water bathing, aquatic exercise and magnetotherapy without peloid therapy. In patients treated with Kolop peloid, clinical parameters (WOMAC pain, joint stiffness, and function) improved significantly more compared to the control group. At the end of the follow-up period, quality of life was significantly better in the peloid-treated group compared to the control group. According to our opinion the more significant improvement observed in the peloid-treated group was caused by the favorable effect of the peloid. We can conclude that Kolop peloid is a possible therapeutic option in the treatment of patients with knee osteoarthritis.

III. According to the systematic review of 18 clinical trials and the metaanalysis of 9 trials by Hungarian authors carried out in Hungary in the field of balneotherapy we can conclude that immersion in mineral water has beneficial effect on clinical parameters especially on pain at rest and on pain on weight bearing. We didn't want to hide our purpose to make use of this paper as a way to improve the image of our country as Hungarian scientists can be proud of their results in the field of balneotherapy.

SUMMARY

Balneotherapy is traditionally used in the treatment of musculoskeletal disorders with chronic pain, especially in the therapy of degenerative musculoskeletal disorders. However, based on the data available according to the metaanalyses performed so far, there is not enough evidence of its effect in the absence of enough studies performed with adequate methodology. However, the therapy of musculoskeletal disorders with chronic pain, within this the therapy of degenerative musculoskeletal disorders, has its own limitations. I found it necessary to perform studies with adequate methods in order to help balneotherapy to take its place in the therapeutic guidelines.

The effects of immersion in mineral water on chronic low back pain and on chronic shoulder pain was studied. The effects of mud hot pack therapy on osteoarthritis of the knee was evaluated in two different ways. Our aim was also to provide an overview of Hungarian research in the field of balneotherapy and to conduct a meta-analysis of the clinical studies meeting the predefined criteria

Our randomized, controlled, single-blind, follow-up pilot study demonstrated the beneficial effect of immersion in high-mineral-content water from Mátraderecske on clinical parameters, quality of life and analgesic and NSAID requirements in patients with chronic low back pain, in comparison to immersion in tap water with the same temperature.

According to our randomized, controlled, single-blind, follow-up pilot study immersion in mineral water combined with exercise and TENS therapy may provide significantly better results than exercise and TENS alone on the clinical parameters of patients suffering from chronic shoulder pain with a possible improvement in the quality of life of patients as well. Our trial is the first study in the English literature evaluating the effect of immersion in mineral water in chronic shoulder pain. The number of patients should be increased

According to our randomized, controlled, double-blind, follow-up pilot study, we have shown that when used in a hot pack, the Neydharting mud has a strong positive effect on the clinical parameters of patients with knee osteoarthritis, and it also caused a clear improvement in quality of life and a decreased need for medications. Our results suggest that most of the effect of hot mud pack therapy might be due to heat. To evaluate the chemical effect by increasing the number of patients, would be promising.

According to our randomized, controlled, single-blind follow-up study in the day hospital care setting showed that Kolop peloid has favorable effect on knee osteoarthritis both in the short and long term. Peloid therapy combined with mineral water bathing, aquatic exercise and magnetotherapy provided significantly better results regarding pain, function and quality of life than mineral water bathing, aquatic exercise and magnetotherapy without peloid therapy.

According to the systematic review of 18 clinical trials and the metaanalysis of 9 trials by Hungarian authors carried out in Hungary in the field of balneotherapy we can conclude that im-

mersion in mineral water has beneficial effect on clinical parameters especially on pain at rest and on pain on weight bearing.

We can conclude that immersion in mineral water and mud hot pack therapy are possible therapeutic options in the treatment of musculoskeletal diseases with chronic pain, especially with degenerative origin. The number of patients should be increased.

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LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVATIONS

ACR	American College of Rheumatology
CI	confidence interval
EQ-5D	EuroQoL five dimensions questionnaire
EQ VAS	EuroQoL visual analogue scale
EULAR	European League Against Rheumatism
g	gram
Hz	hertz
ITT	intention-to-treat
L	liter
mA	milliamper
mg	milligram
mm	millimetre
MCII	minimal clinically important improvement
MDC	minimal detectable change
MPCI	minimum perceptible clinical improvement
NHP	Nottingham Health Profile
NRS	numerical rating scale
NS	non significant
NSAIDs	non-steroidal anti-inflammatory drugs
OARSI	Osteoarthritis Research Society International
ODI	Oswestry Disability Index
p value	probability value
RCT	randomized controlled trial
SD	standard deviation
SF-36	Short Form (36) Health Survey quality of life questionnaires
SMD	standardized mean difference
SPADI	Shoulder Pain and Disability Index
SYSADOA	Symptomatic Slow Acting Drugs in Osteoarthritis
TENS	transcutaneous electrical nerve stimulation
VAS	visual analogue scale
w	Kendall's coefficient
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index

APPENDIX

Photo 1 Mineral water of Mátraderecske (on the left) and tap water (on the right)

Photo 2 The Neydharting mud and the control materia