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REVIEW ARTICLE

Mechanisms of action of spa therapies in rheumatic diseases: what scientific evidence is there?

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Abstract Spa therapy represents a popular treatment for many rheumatic diseases. The mechanisms by which immersion in mineral or thermal water or the application of mud alleviates suffering in rheumatic diseases are not fully understood. The net benefit is probably the result of a combination of factors, with mechanical, thermal and chemical effects among the most prominent ones. Buoyancy, immersion, resistance and temperature all play important roles. According to the gate theory, pain relief may be due to the pressure and temperature of the water on skin; hot stimuli may influence muscle tone and pain intensity, helping to reduce muscle spasm and to increase the pain threshold. Mud-bath therapy increases plasma β-endorphin levels and secretion of corticotrophin, cortisol, growth hormone and prolactin. It has recently been demonstrated that thermal mud-pack therapy induces a reduction in the circulating levels of prostaglandin E2 (PGE2), leukotriene B4 (LTB4), interleukin-1β (IL-1β) and tumour necrosis factor-α (TNF-α), important mediators of inflammation and pain. Spa therapy has been found to cause an increase in insulin-like growth factor-1 (IGF1), which stimulates cartilage metabolism, and transforming growth factor-β (TGF-β). There is also evidence of the positive action of mud-packs and thermal baths on the oxidant/antioxidant system, with a reduction in the release of reactive oxygen (ROS) and nitrogen (RNS) species. Overall, thermal stress has an immunosuppressive effect. Many other non-specific factors may also contribute to the beneficial effects observed after spa therapy in some rheumatic diseases, including effects on cardiovascular risk factors, and changes in the environment, pleasant surroundings and the absence of work duties.

Keywords Spa therapy · Balneotherapy · Mud-packs · Rheumatic diseases · Mechanisms of action

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Introduction

Spa therapy comprises a broad spectrum of therapeutic modalities including hydrotherapy, balneotherapy, physiotherapy, mud-pack therapy and exercise [1, 2]. This therapeutic approach has been successfully used in many European countries, as well as in Japan and Israel, in classical medicine as a cure for various illnesses. Today, it continues to be a popular treatment for many rheumatic diseases (RD) [3] due to their chronic nature, problems related to the use of drugs that often have significant side effects and the occasional lack of valid therapeutic strategies [4–8]. Thousands of years of history and the abundance of spa resorts in many European countries have undoubtedly contributed to the popularity of these therapies.

The aim of spa therapy is to reduce pain, relieve muscle spasms and improve muscle strength and functional mobility [1, 2].

Nevertheless, despite their long history and popularity, spa treatments are still the subject of debate and their role in modern medicine continues to be unclear [9].

The action mechanisms of mud-packs and thermal baths are not fully known, and it is difficult to distinguish the effects of thermal applications from the benefits that could be derived from a stay in a spa environment [1].

In an era of evidence-based medicine, it is necessary to ask what real medical and scientific value these therapies have. The objective of this review is to summarize the currently available information on mechanisms of action and possible effects of spa therapy in RD. We also provide some suggestions for further development in this area.

Mechanisms of action of spa therapy in rheumatic diseases

The mechanisms by which immersion in thermal mineral water or the application of mud packs alleviates suffering in RD are not fully understood. The net benefit is probably the result of a combination of factors, with mechanical, thermal and chemical effects among the most prominent ones [1].

A distinction can be made between the non-specific (hydrotherapeutic in a broad sense) mechanisms common to simple baths in hot tap water and specific (hydromineral and crenotherapeutic) mechanisms, which depend on the chemical and physical properties of the water used. While the former are well known, the latter are difficult to identify and assess [1].

Mechanical effects

Spa therapy may have beneficial effects on muscle tone, joint mobility and pain intensity.

Increased buoyancy and hydrostatic pressure during immersion in thermal mineral water cause many physiological changes. Immersion to the suprasternal notch in spa water (35°C) results in a cascade of reactions including increased diuresis, natriuresis and cardiac output [10–12]. The basis of these physiological effects is considered to be hydrostatic pressure, which forces approximately 700 ml from the lower extremities to the central compartment. Distension of volume receptors by this central hypervolemia is regarded as the trigger for the observed physiological effects [10–12].

Thermal effects

The effects of mud-packs and thermal baths are partially related to temperature. Hot stimuli may influence muscle tone and pain intensity, helping to reduce muscle spasm and to increase the pain threshold in nerve endings. According to the "gate theory", pain relief may be due to the temperature and hydrostatic pressure of water on the skin [13].

Thermal stress provokes a series of neuroendocrine reactions. In particular, the heat stimulates the release of adrenocorticotropic hormone (ACTH), cortisol, prolactin and growth hormone (GH), although it does not alter the circadian rhythm of these hormones [14].

The effect of thermal stress on the hypothalamus–pituitary–adrenal axis seems to be particularly important for the anti-edemigenous and anti-inflammatory actions of corticosteroids, as well as for the frequent alteration of the axis during some rheumatic diseases [15]. The increase in beta-endorphin demonstrated to occur with various spa therapy techniques [16–19] has an analgesic and antispastic effect that is particularly important in patients for whom pain is the prevalent symptom. Interestingly, it has been revealed that the application of mature thermal mud in healthy individuals brings about a rapid increase in plasma beta-endorphin, which returns to pre-treatment levels within the period of so-called thermal reaction [19]. This increase in beta-endorphin is probably the key factor in the mechanism of individual tolerance to thermal mud baths.

Recent data have demonstrated the possibility that normal keratinocytes can produce and secrete a precursor pro-opiomelanocortin (POMC) following various stimuli (e.g. ultraviolet rays, thermal stimuli) which is the common precursor of various endorphins [20]. This finding allows us to formulate the fascinating hypothesis that ultraviolet radiation or thermal stimuli could be used to condition the skin's production of opioid peptides, thus altering the personal emotional sphere or pain threshold. If we add that ß-endorphin also has immunomodulatory effects [21], the hypothesis of a close correlation between spa therapies and the psychoneuroendocrine system becomes increasingly convincing.

Furthermore, hyperthermia plays an important role in immune system function.

Hyperthermia also has many effects on granulocytes. Heat increases their mobility, phagocytic and bactericidal properties and enzymatic activity [1].

Furthermore, thermal stimulation increases the extensibility of collagen-rich tissues, such as tendons, fasciae and articular capsules, which may improve the range of motion of joints [1].

The effects described make it possible to break the vicious circle of pain–muscle contraction–altered joint dynamics–pain that characterizes many chronic arthropathies. The reduction in muscle tone and better use of joints represent just two of the most important elements that show the medium- and long-term beneficial effects documented in various clinical studies [22–31].

Chemical effects

The chemical effects of mud packs and balneotherapy are less clear than the physical effects. In theory, it cannot be excluded that the organic substances or minerals in water

or mud, sometimes present in trace amounts, can be absorbed through the skin and then act at a systemic level. However, experimental evidence available in this field is scarce. Shani et al. [32] documented a significant increase in serum concentrations of bromine, rubidium, calcium and zinc in patients with psoriatic arthritis who bathed in the Dead Sea. Solute penetration is presumably influenced by the length of bathing time, the temperature of the thermal water, its composition and other factors, some of which may still be unknown. An in vitro study has demonstrated that substances in aqueous mud extracts can permeate through human full-thickness skin in quantities that have definite effects on spontaneous contractile activity of smooth muscle tissue [33]. Furthermore, it has been reported that the direct application of mud pack has greater clinical effects than the application of nylon-covered mud pack in patients with knee osteoarthritis (OA) [34]. This finding implies a contribution of the chemical properties of the mud to the overall beneficial effects of mud-pack treatment, thus ruling out that the effects are linked exclusively to the action of heat.

Immunologic aspects

Since sulphur spa baths have been successfully used in various skin immuno-mediated afflictions, it has been suggested that absorption through the skin of trace elements present in mineral water and mud packs may affect the immune system [35].

Overall, thermal stress has an immunosuppressive effect. With regard to hyperthermia, a stimulatory effect of the immune response appears to prevail at a moderate increase in local skin temperature, with increases in the proinflammatory cytokines interleukin (IL)-6 [36] and IL-1ß [37], whereas higher temperatures (40–41°C) apparently suppress immune functions [38, 39].

A significant reduction in the circulating levels of T lymphocytes has been demonstrated in healthy volunteers treated with hyperthermal baths [1] and in patients with respiratory and cutaneous atopy [40]. Hyperthermia-induced T lymphocytopenia and eosinopenia may result from a redistribution of the cells, probably due to the increase in ACTH and cortisol provoked by thermal stress [14].

In vitro studies have demonstrated that sulphurous spa waters have a dose-dependent inhibitory effect on the blast transformation and proliferation of T lymphocytes obtained from peripheral blood in both healthy subjects and subjects affected by chronic inflammatory diseases [40]. On the other hand, immersion in thermal waters at a temperature of 40°C reduces the lymphocyte response to phytohaemoagglutinin [41]. Sulphurous spa waters also seem to exert a potent inhibitory action on the production of cytokines, especially IL-2 and interferon gamma (IFN-γ). As these cytokines are mainly produced by CD4+ lymphocytes, it can be hypothesized that memory T cells are the principal target of sulphur-rich waters. The application of sulphurous waters reduces the capacity of memory T cells to proliferate and produce cytokines, thus resulting in an alteration of immune response [42]. Hyperthermia-induced alteration of the cytokine milieu has been recently confirmed in patients affected by ankylosing spondylitis (AS) [43]. Tarner et al. showed that the serum levels of tumour necrosis factor (TNF)-α, IL-1β and IL-6 which were measured before, during and after whole-body hyperthermia were significantly reduced in patients with AS, whereas the changes in healthy subjects were not statistically significant.

Anti-inflammatory and chondroprotective aspects

Recent studies have shown a reduction in the circulating levels of prostaglandin E2 (PGE2) and leukotriene B4 (LTB4), important mediators of inflammation and pain, in patients suffering from OA or fibromyalgia who undergo mud packs or balneotherapy [44, 45] (Table 1).

Crenotherapy also affects the synthesis of various cytokines involved in the ongoing chondrolysis and

Table 1 Effect of thermal mineral mud baths on various mediators or factor of immune response, inflammation and chondrolysis

Reduction in circulating levels of PGE2 and LTB4 in patients with OA and fibromyalgia [Ref. 44, 45]
Reduction in TNF-α, IL-6 and IL-1β circulating levels in patients with AS caused by whole-body hyperthermia (41°) [Ref. 43, 46–48]
Reduction in the release of ROS and the (RNS) peroxynitrite by PMNs stimulated with N-formyl-methionyl-leucyl-phenylalanine and phorbol-12-myristate-13-acetate [Ref. 58]
Decrease in NO circulating levels in the sera of subjects with OA undergoing mud baths [Ref. 62]
Increase in circulating levels of IGF1 in patients with OA undergoing mud baths [Ref. 52]
Increase in circulating levels of transforming growth factor-beta (TGF-ß) has been found in patients with AS after a combined spa-exercise therapy (exercise, hyperthermia and exposure to low doses of radon) [Ref. 53]

PGE_2 prostaglandin E_2, *LTB_4* leukotriene B_4, *OA* osteoarthritis, *TNF-α* tumour necrosis factor-α, *IL-6* interleukin-6, *IL-1β* interleukin-1β, *AS* ankylosing spondylitis, *ROS* reactive oxygen species, *RNS* reactive nitrogen species, *PMNs* polymorphonucleate leukocytes, *NO* nitric oxide, *IGF1* insulin-like growth factor 1, *TGF-β* transforming growth factor-beta

inflammation in RD; in fact, a reduction in the cytokines IL-1ß and TNF-α and the soluble receptors of the latter has been demonstrated following a cycle of mud-bath therapy (temperature > 41°C) in patients with OA [46–48] (Table 1).

Several studies have provided evidence for a significant role of matrix metalloproteinases (MMPs), particularly MMP-3 or stromelysin-1, produced by activated chondrocytes and other cell types in the development of cartilage degradation in joint diseases [49, 50]. A recent study by Bellometti et al. [51] showed that MMP-3 serum levels were significantly reduced by mud-bath therapy in patients with OA.

Cycles of mud applications and balneotherapy also bring about an increase in some growth factors, such as insulin-like growth factor 1 (IGF1) [47], which stimulates cartilage anabolism [52]. Furthermore, a significant increase in the circulating levels of transforming growth factor-beta (TGF-ß) has been found in patients with AS after combined spa-exercise therapy (exercise, hyperthermia and exposure to low doses of radon) [53] (Table 1). TGF-ß is a very potent immunomodulating and anti-inflammatory cytokine which plays a major role in tissue healing, bone remodelling and fibrosis [54, 55].

Among the various factors responsible for inflammatory and degenerative phenomena in joints in various forms of RD, reactive oxygen species (ROS) and nitric oxide (NO) should be taken into consideration [56, 57].

Sulphurous waters have been demonstrated to have an antioxidant effect in vitro; in fact, the incubation in sulphurous mineral water significantly reduces the release of ROS and the reactive nitrogen species (RNS) peroxynitrite by polymorphonucleate leukocytes (PMNs) stimulated by N-formyl-methionyl-leucyl-phenylalanine and phorbol-12-myristate-13-acetate [58]. Various studies in humans have highlighted the positive action of mud packs and thermal baths, especially sulphurous ones, on the oxidant/antioxidant system. Grabski et al. [59] reported the reduction in superoxide dismutase (SOD) activity in patients with rheumatoid arthritis (RA) undergoing treatment with sulphuric water. Eckmekcioglu et al. [60] demonstrated that 3 weeks of sulphur baths can reduce the antioxidative defence system (SOD and glutathione (GSH) peroxidase) in the blood of patients with OA. They suggested two possible causes for the decline of these enzyme activities: either as a consequence of reduced oxidative stress during sulphur therapy leading to a lower expression of these enzymes or as an enhanced generation of superoxide radicals exhausting the superoxide-scavenging enzyme. Bender et al. [61] demonstrated that therapeutic baths in mineral water reduced the activity of catalase, SOD, malondialdehyde (MDA) and GSH peroxidase. Other authors have observed a significant decrease in NO and myeloperoxidase (MPO) and a slight increase in GSH peroxidase in the sera of subjects with OA undergoing cycles of mud applications and balneotherapy [62]. The slight increase in GSH peroxidase does not correlate with the reduction in the other biochemical markers, suggesting that thermal mud possesses various different mechanisms of action.

In a recent study, we assessed the possible modifications of plasma levels of leptin and adiponectin in patients with OA treated with a cycle of spa therapy [63]. Our data showed a slight but not significant increase in plasma leptin concentrations and a significant decrease in serum adiponectin levels at the end of mud-bath therapy cycle. These adipocytokines play an important role in the pathophysiology of OA [64, 65]. In particular, there is some evidence that adiponectin in skeletal joints may have proinflammatory effects and may be involved in cartilage degradation [64, 66]. In view of these recent findings, the decrease in adiponectin after spa therapy demonstrated in our study may play a protective role in OA.

Experimental studies in animal models of arthritis corroborate the evidence of beneficial effects of mud-bath therapy on inflammatory and degenerative joint diseases. Cozzi et al. [67] have recently demonstrated an anti-inflammatory effect of mud-bath applications in Freund's adjuvant-induced arthritis in rats. Following the application of crenotherapy, a reduction in oedema in the rat paws (measured by plethysmometry) was accompanied by a significant reduction in the levels of circulating TNF-α and IL-1β. In 2007, Britschka et al. [68] confirmed the anti-inflammatory and chondroprotective effects of the application of mud in Zymosan-induced arthritis in rats, by performing histological analysis on synovial tissues and cartilage taken from the sacrificed animals on day 21 of treatment. Examination of the synovial tissue in particular revealed reduced hyperplasia of the lining, reduced vascularization and cellular infiltration in the group of rats treated with mud applications, in contrast to the group of rats treated with simple heated tap water and the untreated (control) group of rats. With regard to cartilage, there was a macroscopically visible reduction in erosive lesions as well as an increase in chondrocyte density and collagen and proteoglycan content only in the mud-treated animals (Figs. 1, 2).

Other aspects

Many other non-specific factors may also contribute to the beneficial effects observed after spa therapy in some RDs, including effects on cardiovascular risk factors.

The lipid-normalizing effects of mud applications and balneotherapy, especially with sulphurous waters, have been reported for decades. The results of such research

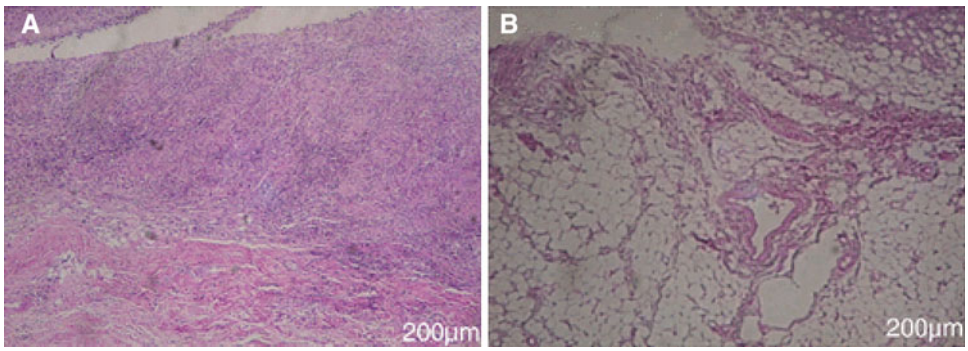

Fig. 1 The synovium from control animals stained with H&E is depicted in (**a**). Sub-synovial infiltration and maintenance of the synovial lining could be observed in samples obtained from mud-treated rats (**b**). Original magnification ×100 (with kind permission of Dr. Britschka ZMN and Professor de Mello SBV [Ref. 68])

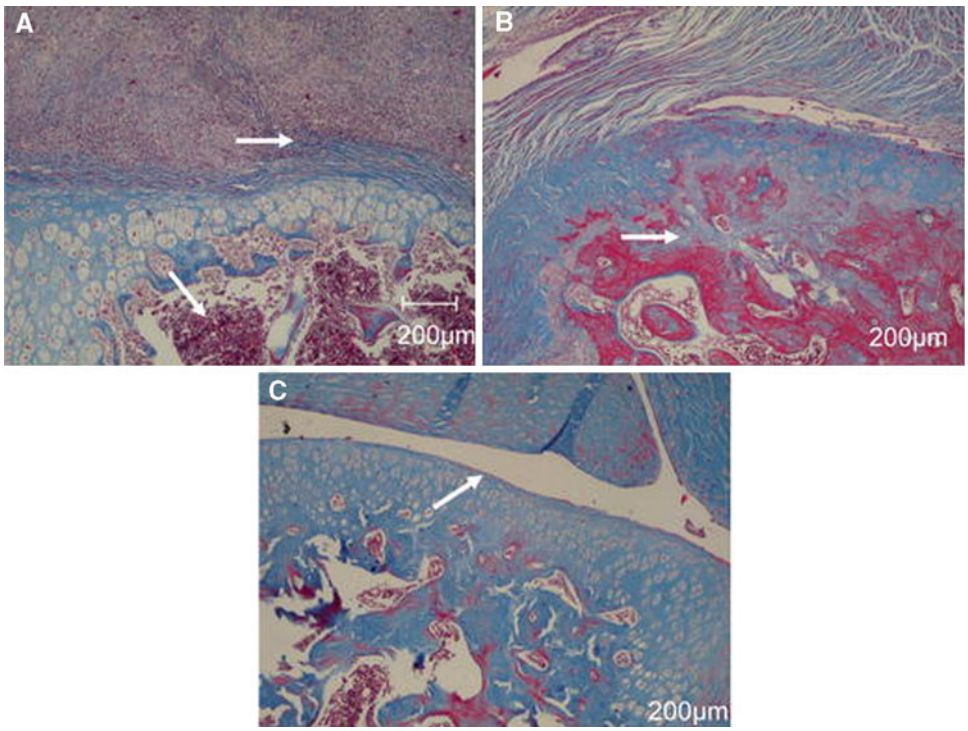

Fig. 2 Photomicrographs of knee joint from rats with Zy-IA in the 21st day stained with Masson trichrome. The pattern observed in untreated animals is shown in (**a**) and that in the water-treated group in (**b**). *Arrows* indicate cartilage erosion with the development of fibrous cartilage, overgrown pannus and subchondral bone damage. **c** The pattern of the joint from mud-treated group, *arrow* shows the maintenance of the articular space and cartilage tissue. Original magnification ×100 (with kind permission of Dr.Britschka ZMN and Professor de Mello SBV [Ref. 68])

have documented reductions in total cholesterol, triglycerides and non-esterified cholesterol and a significant increase in HDL cholesterol [69, 70].

More recently, attention has focused on plasma homocysteine, a risk factor for coronary heart disease, congestive heart failure, systolic hypertension, artherothrombotic events, complications in diabetes mellitus, cancer and oxidative stress [71–75]. A significant reduction in plasma homocysteine has been demonstrated in OA patients after a cycle of sulphurous thermal baths [76].

Recently Oláh et al. [77] explored changes in several cardiovascular risk factors in a group of patients suffering from degenerative musculoskeletal disorders subjected to a cycle of balneotherapy. The authors showed a statistically significant and lasting (3 months after the cycle of balneotherapy) decrease in serum levels of C-reactive protein (CRP) in patients treated with mineral thermal baths.

The reduction in cardiovascular risk factors through the use of mud packs and balneotherapy is especially important considering the clear and much stressed association between various RDs and atherosclerotic processes [78].

Finally, other elements need to be taken into consideration concerning the mechanisms of action of mud applications and balneotherapy in RD, such as the particular climatic and environmental conditions of spas and the fact that people rest more and are far from daily stress during stays at spa resorts [1, 2].

Unresolved issues concerning the mechanisms of action of spa therapies

Although the data presented are stimulating, it is impossible to ignore the existence of a complex series of

problems and uncertainties that prevent spa therapies from gaining the full consensus of the scientific community [9]. One of the critical points is the controversial problem of the absorption of the minerals dissolved in thermal waters, i.e. the demonstration of specific effects other than those linked to the simple action of heat. Unfortunately, few studies have been conducted on this topic and little is known about the specific effects of various mineral waters. It is still not clear which elements are essential and what the ideal concentration of each element is in order to attain an optimal response to treatment. It remains to be clarified which mineral waters are most suitable for various diseases and whether the different components exert specific actions. Such evidence would lead to a specialization of spa resorts, which could finally target their therapies more accurately and rationally.

Conclusions

In this review, we have underlined the effects of mud applications and balneotherapy on various mediators or factors of immune response, inflammation and chondrolysis. However, the results reported only refer to short-term modifications of these factors, lasting until the end of the cycle, and little is known of the possible long-term effects. This is a key element in seeking to explain the persistence of the symptomatic benefit induced by such therapies in some RDs, as shown in long-term controlled clinical trials [22–31].

The evidence gained is therefore important but nonetheless only preliminary and awaits confirmation by more in-depth studies conducted according to the canons of modern scientific research. In order to develop Thermal Medicine as a valid and recognized field, a series of studies aimed at providing ever more precise therapeutic indications and clarifying the mechanisms of action and the effects deriving from the application of thermal treatments are imperative.

This is the only way for Thermal Medicine to emerge from the restrictive environment of alternative or "miracle" therapies and free itself of the scepticism of many doctors and patients, gaining the scientific respect that it truly deserves.

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