

Rheumatic Diseases and Molecular Physical Medicine – New Aspects

Rheumatische Erkrankungen und molekulare physikalische Medizin – Neue Aspekte

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ABSTRACT

A multimodal treatment of rheumatic diseases without physical medicine is incomplete. However, the mechanisms underlying the beneficial effects of physical medicine are only partially understood. Modern molecular medicine offers new insights into pivotal mechanisms and mediators of the inflammatory process and into interactions between cells of the immune system and bone cells. Investigating the potential influences of different methods of physical medicine on the central regulatory processes of inflammatory rheumatic diseases is of great interest, highly fascinating and opens up new avenues of research for the future. This article focuses on the novel results of molecular physical medicine in rheumatic diseases and osteoporosis.

ZUSAMMENFASSUNG

Eine multimodale Therapie von rheumatischen Erkrankungen ohne physikalisch-medizinische Maßnahmen ist stets unvollständig. Die Wirkungsmechanismen, die der klinischen Verbesserung durch physikalische Maßnahmen zugrunde liegen, sind bisher nur teilweise bekannt. Methoden der molekularen Medizin ermöglichen es inzwischen zentrale Botenstoffe des inflammatorischen Geschehens – die u. a. für die Wechselbeziehungen zwischen Knochen- und Immunzellen von zentraler Bedeutung sind – und deren Beeinflussung durch Applikation physikalischer Therapiemaßnahmen zu analysieren. Der Eingriff in dieses zentrale Regulationssystem bei rheumatischen Erkrankungen und Osteoporose durch Physiotherapeutika ist spannend und faszinierend zugleich und bietet zukünftig ein großes Forschungsfeld. Der vorliegende Artikel bietet einen Überblick über erste Resultate auf diesem neuen Forschungsfeld der molekularen physikalischen Medizin.

Physical Medicine in the Context of Rheumatic Diseases

Methods of physical medicine have played an invaluable role in the therapeutic concept of rheumatic diseases far into the second half of the past century – when drug-based treatments were limited and toxic. Since then, the significance of physical medicine has unfortunately been outshined by the rapid therapeutic success of new

Disease Modifying Antirheumatic Drugs (DMARDs) and the biologics (so-called “anti-cytokine therapeutics”) in the past 20 years. Nevertheless, physical medicine plays a still central role in the multimodal therapy of rheumatic diseases, and is a key component of therapeutic guidelines [1–3].

According to current data from the German Collaborative Arthritis Centers for the treatment of rheumatoid arthritis (RA),

35.9 % of the patients were in remission while 19.2 % had low, 37.1 % moderate and 7.8 % high levels of disease activity based on the Disease Activity Score 28 (DAS28) [4]. The remission rate increased by 8–10 % only among patients with longer disease durations in the years 2007–2014 while the rate remained unchanged in disease durations of shorter than 2 years. Between 51.5–70 % light to severe function impairments (Funktionsfragebogen Hannover–FFbH < 75) could also be measured in patients with ankylosing spondylitis in the years 2007–2014 despite up to late pharmacological treatments [5]. Based on this shortcoming, an early intensification of therapy including physical therapy modules is fully justified to further reduce the disease activity, and the overall burden of disease of the affected patients.

Consequences of Disease for Patients with Inflammatory Rheumatic Diseases

The International Classification of Functioning, Disability, and Health (ICF) of the World Health Organization provide the basis for systematic disease management for chronic diseases [6]. The ICF bases the classification on an integrative biopsychosocial approach. It also incorporates, on one hand, function capability and impairment with the components body functions and structures, activity and participation as well as on the other hand, context factors with the components environment and personalized factors. Pain and accompanying musculoskeletal dysfunction frequently cause impairments in the ICF component daily activities as well as participation in social life [7].

Thus, distinct daily disablements (impairment of function capacity based on the function score FFbH at 70 % or less) are present in 4 out of 10 patients with rheumatoid arthritis and ankylosing spondylitis whereby nearly half of the patients experience severe functional impairments (≤ 50 % in FFbH) [8]. The function capacity that can be therapeutically modified or compensated by physical therapy is of key significance for participation in professional life: approximately 50 % of patients with inflammatory rheumatic diseases with severe function impairment from RA or AS receive a disability pension in contrast to only every fifth to tenth patient with mild function impairment (> 70 % FFbH) [8].

Current Challenges of Physical Medicine

At present, physical medicine is faced with 2 major challenges: on one hand, it is no longer necessary to rely solely on tradition and experience but rather to accept the challenge of modern evidence-based medicine and consequently provide the respective scientific knowledge and evidence of efficiency. On the other hand, in an era of increasing budget of simultaneously rising costs of medicine, there is hardly any financial manoeuvring space so attention must also be paid to economic restrictions.

Molecular physical medicine can definitively contribute to the solution of both of these tasks. Based on research of the molecular and cellular biological effects of physical therapy on the human body, the pathophysiological processes identified by modern im-

munological basic research and by the comparison of medications, molecular physical medicine can successfully prove its efficiency as well as deliver the required scientific evidence [9, 10].

As the effects of differentially indicative physical therapy treatments, in particular, on specific mechanisms of the inflammatory occurrences and on immunocompetent cells are widely unknown, the intervention of physiotherapeutics into this central regulatory system in rheumatic diseases is exciting and likewise fascinating and presents a large research field for today as well as the future.

To illustrate the actual interesting and very promising results of this new discipline of molecular physical medicine for rheumatic symptoms several examples are outlined below.

Efficiency and Molecular Effects by Thermotherapy

At the end of the 1970s, initial molecular findings in terms of a pro-inflammatory effect of prostaglandin stimulation have been associated with cryotherapy [11]. In a pilot study of whole body cryotherapy, a significant decrease in pro-inflammatory cytokines as well as improvements in activity and function parameters in inflammatory rheumatic diseases could be objectified [12]. A reduction of prostaglandin E2 and leukotriene B4 due to local heat application was described [13]. Additional studies could prove that it is possible to influence the cytokine level with both local thermotherapy and whole body hyperthermia (► **Table 1**, [14]).

By now, it could be proven that an intensive local and systemic hyperthermia (target core temperature > 41 °C) inherits an immunosuppressive effect whereas a mild, moderate systemic hyperthermia (target core temperature 38–40 °C) induces immunomodulating and immunostimulating effects [15].

When studying the molecular effects of a mild systemic hyperthermia in rheumatic diseases in humans, it is of great interest in the era of medicinal biological therapy, directed, against pro-inflammatory cytokines such as IL-1, IL-6 and TNF- α , whether and how these cytokines are altered and whether therapy at a cellular and molecular level has an immunostimulating or anti-inflammatory effect.

► **Table 1** Heat application and changes in the cytokine level [overview in 14].

- Interleukin-1 synthesis is downregulated by light thermal stress.
- TNF-alpha induced dissolution of WEHI 175 cells is antagonized by hyperthermia.
- Interleukin-1 activity is increased in skin heated from the lymphatic system.
- Interleukin-1 production is augmented through whole body hyperthermia in a murine model (40 °C, 60 min).
- Rises in interleukin-6 levels are achieved with hot paraffin packs.
- Interleukin-1 is reduced by serial hot mud packs.
- Immunoglobulin production of mononuclear blood cells is stimulated by mild hyperthermia in humans.
- TNF-alpha increases during a spa treatment in an acratotherm in osteoarthritis patients.

Whole Body Hyperthermia by means of Hyperthermal Bath, Water-filtered Infra-red A Radiation, Radon Therapy and Healing Mud Baths

The mild systemic hyperthermia in the form of a hyperthermal bath has already been successfully applied as a so-called passive mild whole body hyperthermia in ankylosing spondylitis (AS) since the end of the 1960s. The systemic application of this therapy treatment has the advantage that deeper structures such as, e. g. the vertebral column, can also be reached. When observing empirically the physical medicine, the passive mild whole body hyperthermia principle appeared to act by muscle detension, increase of blood circulation (hyperperfusion) and analgesic effect. When viewing this from the perspective of molecular physical medicine, the focus is, however, on underlying potential cellular and molecular mechanisms.

In an explorative study [16], 12 male AS patients with sole NSAR medication and 12 healthy males of comparable age underwent a series of passive mild whole body hyperthermia in hyperthermal baths (a total of 9 applications, target core body temperature 38.5 °C). Albeit the analysis of the peripheral T- and B-lymphocytes – as a correlate to a possible immunostimulation and the systemic cortisol level as a correlate to a possible hyperthermia induced stress reaction did not yield significant differences either before or at different points during and after the serial passive mild whole body hyperthermia. In contrast, the result of the analysis of the systemic cytokine level was surprising [17]: the pro-inflammatory cytokines TNF- α , IL-1 β and IL-6 in the AS patients exhibited significantly reduced serum levels at all measuring times up to 24 h after the last hyperthermal bath in comparison to the healthy control group. Depending on the cytokine, the reduction here was between 40–50 % of the initial level prior to the serial passive mild whole body hyperthermia.

In the meantime, improvements at the clinical level (e. g. parameters of activity, function and, subsequently the functional health) as well as at the molecular level (pro- and anti-inflammatory cytokines) could be objectified in inflammatory rheumatic and degenerative diseases in a series of studies on whole body hyperthermia using a variety of means (water-filtered Infrared A radiation [18, 19], radon therapy [20], and healing mud baths [21]) in serial application (summary in ► **Table 2**). At the molecular level, an anti-inflammatory modulation of the cytokine profile was common in all these studies.

Taken together, the results of these hyperthermia studies illustrate that a mild whole body hyperthermia clinically induces a notable amelioration of rheumatic symptoms, reflected by the molecular level. However, different intensities and modalities of a hyperthermia obviously exert a different effect on various molecular inflammation mediators as well.

Influence of the Molecular Mechanisms of Bone Metabolism by means of Whole Body Hyperthermia and Physiotherapy

In addition to the effects on the proinflammatory cytokines of the immune system, a whole body hyperthermia also influences additional molecular mechanisms. This includes the central molecular mechanism of bone metabolism of the RANK/RANKL/OPG system. The soluble mediator receptor activator of nuclear factor- κ B ligand (RANKL) which is primarily secreted from mesenchymal cells and osteoblasts mediates an activation of the osteoclasts or differentiation of the osteoclast progenitors via binding to the membrane-bound receptor RANK, which is expressed on osteoclasts and their progenitor cells and thereby transmits the stimulation of the bone resorption. The activating effect of RANKL is counterbalanced by osteoprotegerin (OPG), in which OPG as soluble receptor without a signaling effect (so-called decoy receptor) competitively binds and thereby inactivates RANKL. It could be shown that an increase of the RANKL/OPG ratio in the serum induces a measurable imbalance in the RANK/RANKL/OPG system which is crucial in both primary as well as secondary osteoporosis.

Inflammation-induced secondary osteoporosis is separated in an increased production and release of RANKL via activated inflammatory and immune cells. In this process, RANKL represents a central osteoimmunological link in inflammatory rheumatic diseases which has been confirmed by animal models of RA and spondyloarthritides on the basis of an increase in the RANKL/OPG ratio in osteodestructive phases.

In the meantime, studies on AS [20, 22, 23] and osteoarthritis [23] using serial radon therapy – whole body hyperthermia (radon adit in Bad Gastein-Böckstein, Austria) using could show that molecular mechanisms of inflammation induced osteoporosis are downregulated, along with molecular mechanisms of the underlying inflammation. Among other parameters, the patients with AS displayed a significant decrease in the RANKL/OPG ratio by shifting the molecular mechanisms of the bone metabolism to an osteoanabolic state.

Similar results could also be achieved in patients with rheumatoid arthritis (RA) [24]. Here, a significant reduction of the anti-CCP antibody level was also achieved. Based on the fact that the anti-CCP antibodies correlate with bone destruction in RA and anti-CCP antibodies directly induce the osteoclastogenesis and bone resorption via adaptive immune system and bone resorption, an additional osteoprotective mechanism at the molecular level can therefore be postulated.

When summarizing the effects on different patient cohorts, it can be hypothesized that a serial radon and whole body hyperthermia therapy reduces the systemic RANKL secretion of, amongst others, the T-cells. Consistent with this, the significant decrease in the TNF- α serum level can also be interpreted as a reduced expression via T-cells and other immune cells.

Moreover, in a randomized study applying a once weekly standardized training program with an intervention group with consistent axial bone density values, not only a significant functional improvement and reduction in pain but also a significant increase in bone density on the right femoral neck in osteoporosis could be prospectively achieved over 2 years. A significant reduction of the

► **Table 2** Summary of hyperthermia studies with molecular results.

Authors	Lange U et al. 2014 [18]	Lange U et al. 2017 [19]	Dischereit G et al. 2014 [20]	Dischereit G et al. 2017 [21]	Lange U et al. 2016 [24]
Disease(s)	Psoriatic Arthritis (PSA)	Ankylosing Spondylitis (AS)	Ankylosing Spondylitis(AS), Osteoarthritis (OA)	Osteoarthritis (OA of the hip and/or knee)	Rheumatoid Arthritis (RA), Osteoarthritis (OA)
Physical interventions	Serial water-filtered infrared A radiation (wIRAR), target body core temperature 38.5–39 °C	Serial water-filtered infrared A radiation (wIRAR), target body core temperature 38.5–39 °C	Serial radon hyperthermia in a therapeutic addit (sRH, 12 applications in 3 weeks)	Serial mud baths (sMB)	Serial radon hyperthermia in a therapeutic addit (sRH, 12 applications in 3 weeks)
Patients	n = 15 PSA patients with multimodal physical therapy (MPT) –control group (KG) n = 20 PSA patients with MPT and 6 times wIRAR application in 8 days – intervention group (IG)	n = 15 AS patients with MPT – control group (KG) n = 20 AS patients with MPT and 6 times wIRAR application in 8 days – intervention group (IG)	n = 24 AS patients n = 24 OA patients	n = 22 patients with OA and MPT n = 18 patients with OA and MPT and sMB (9 applications in 3 weeks)	n = 25 RA patients n = 24 OA patients
Observation period	Up to 6 months after the last wIRAR application	Up to 3 months after the last wIRAR application	Up to 3 months after last radon hyperthermia application	Clinical parameters up to 3 months after last mud bath	Lasting up to 3 months after last sRH application
Study design	Randomized, prospective	Randomized, prospective	Prospective	Randomized, prospective	Prospective
Clinical results	IG: significant improvement lasting up to 6 months of pain [VAS] (p < 0.04) HAQ (p < 0.01) DAS28 (p < 0.01) PASI without significant changes KG: no significant changes of pain, and DAS28. Significant improvement of the HAQ after 3 months vs. baseline (p < 0.02)	IG: significant improvement lasting up to 3 months of pain [VAS] (p < 0.014) BASDAI (p < 0.039) BASFI (p < 0.048) KG: no significant changes of VAS, BASDAI, BASFI	AS: significant pain reduction after sRH, lasting up to 3 months (p < 0.005, respectively). Significant improvement of the BASDAI lasting up to 3 months (p < 0.003), and the BAS-G after 3 months (p < 0.005) OA: significant pain reduction after 3 months vs. baseline (p < 0.005)	OA plus sMB presented right after the last mud bath a significant improvement of the HAQ (p < 0.01) and FFBH (p < 0.01), and also a significant reduction of pain lasting up to 3 months (p < 0.01) and significant improvement of the WOMAC lasting up to 3 months (p < 0.037)	
Molecular effects	IG: stable cytokine profile of TNF-α, IL-1β, and IL-6 KG: right after wIRAR significant decrease of TNF-α (p < 0.01), and after 3 months significant increase (p < 0.008)	IG: significant decrease after 3 months vs. baseline of IL-1β (p < 0.02) TNF-α (p < 0.012) KG: no significant changes	AS: significant reduction of the RANKL/OPG-ratio (p < 0.005) OA: significant reduction of TNF-α (p < 0.0005)	Patients with OA and sMB showed a significant reduction of IL-1β (p < 0.001) and a significant increase of IL-10 (p < 0.001)	RA: significant reduction of the RANKL/OPG-ratio (p < 0.01), ACPA (p < 0.001), and TNF-α (p < 0.001) OA: significant reduction of TNF-α (p < 0.001)

bone resorption marker crosslaps and a significant increase of the bone formation marker osteocalcin could also been seen as a molecular correlate of this osteoanabolic results [25].

In another short study [26] of 20 patients with spondyloarthritis and an indication for a cost-intensive TNF-blockade therapy, a strong economic effect was successfully rendered for the first time through regular physiotherapy over 4 months and a follow-up of 6 months. In this study, the patients received etanercept at half of the standard dose combined with intensive physiotherapy (3 × 45 min sessions per week). By this, a 40 % improvement could be seen in 50 % of the patients after 4 months of treatment according to the criteria of the Assessment of SpondyloArthritis Group (ASAS 40 response). The efficiency of etanercept in a full dose resulted in an ASAS 40 response of 42 % only after 6 months. From socioeconomic aspects, considering the German market prices, a total cost saving of ca. 76000 € could be achieved with the combination therapy – in comparison to the full biologic therapy – in this study. The results indicate also that adequate physiotherapy has a substantial positive influence on the cytokine-transmitted disease mechanisms.

Conclusions for the Practice

- Methods of molecular medicine facilitate the analysis of central messenger molecules of inflammatory processes – which, among other factors, are critical for the interaction between cells of the immune systems and bone cells.
- Physiotherapeutical measures cause significant effects on inflammatory processes and bone metabolism, which correlate to clinical parameters.
- The available results provide explanations for the physiotherapeutical modes of action at the molecular level. As a result, this moves physical medicine from an empirical, deductive discipline to an evidence-based discipline.
- The previous studies of molecular physical medicine emphasize the necessity of physical treatment measures in a multi-mode treatment plan for rheumatic diseases.
- Molecular physical medicine is economic and potentially cost saving reducing the costs of expensive pharmacological therapy.

Conflicts of Interest

The authors have no conflicts of interest.

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