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Research article

Exercise-Induced Hydrogen Sulfide Biosignaling Functional Relevance for Rehabilitation and Balneotherapy – Study protocol

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Abstract: Hydrogen sulfide (H_2S) is an endogenous gasotransmitter increasingly recognized as a biologically active biosignal involved in vascular regulation, redox homeostasis, mitochondrial function, and inflammatory control. Physical exercise is a central intervention in physical and rehabilitation medicine, capable of activating molecular signaling pathways that overlap with hydrogen sulfide–dependent mechanisms. In parallel, sulfurous balneotherapy provides exogenous low-dose hydrogen sulfide exposure and is widely used in rehabilitation practice. However, the role of hydrogen sulfide as a mediator of exercise-induced functional adaptation and its potential modulation through balneotherapy has not been systematically investigated in clinical rehabilitation settings. The primary objective of this study is to evaluate the role of exercise-induced hydrogen sulfide–related biosignaling in functional adaptation during rehabilitation. Secondary objectives include assessing whether the addition of sulfurous balneotherapy enhances functional outcomes and modulates biomarkers related to oxidative stress and inflammation, as surrogate indicators of hydrogen sulfide–dependent signaling pathways. This protocol describes a prospective, controlled, parallel-group clinical trial to be conducted in a balneological rehabilitation center. Approximately 60 adults with chronic musculoskeletal disorders will be recruited and allocated to either a therapeutic exercise–only group or a combined intervention group receiving therapeutic exercise plus sulfurous balneotherapy. The intervention period will last 14 days. Functional outcomes will include validated performance-based and patient-reported measures of physical function and pain. Biological outcomes will include systemic markers of oxidative stress and inflammation assessed at baseline and post-intervention. Statistical analyses will be planned to compare within- and between-group changes and to explore associations between functional and biological outcomes.

Keywords: Hydrogen sulfide; Biosignaling; physical exercise; rehabilitation; balneotherapy; functional adaptation

1. Introduction

Physical exercise is a core therapeutic modality in physical and rehabilitation medicine (PRM), with established efficacy in improving functional capacity, reducing pain, and enhancing quality of life across a broad spectrum of chronic musculoskeletal and degenerative conditions [1]. Beyond its mechanical and neuromuscular effects, exercise elicits complex biological responses involving vascular regulation,

mitochondrial adaptation, redox signaling, and immune modulation [2]. These molecular and cellular adaptations are particularly relevant in rehabilitation populations, where chronic inflammation, endothelial dysfunction, and impaired bioenergetics often limit functional recovery [3].

Hydrogen sulfide (H_2S) has emerged as a major endogenous gaseous signaling molecule, or gasotransmitter, with pleiotropic biological effects [4–6]. Together with nitric oxide and carbon monoxide, H_2S constitutes a distinct class of biosignals that regulate fundamental physiological processes [7,8]. In tissues relevant to rehabilitation—such as skeletal muscle, vascular endothelium, and the nervous system—H_2S modulates blood flow, mitochondrial function, oxidative balance, and inflammatory responses. These effects position hydrogen sulfide at the intersection of molecular biology and functional adaptation [9–11].

Sulfurous balneotherapy is a long-standing therapeutic intervention in PRM and balneology [12]. Sulfurous mineral waters contain bioavailable forms of hydrogen sulfide that can be absorbed through the skin and respiratory tract during therapeutic exposure [13,14]. Clinical observations and controlled studies have reported beneficial effects of sulfurous balneotherapy on pain, joint mobility, and functional outcomes in patients with musculoskeletal disorders. However, the molecular mechanisms underlying these clinical effects, particularly when combined with exercise-based rehabilitation, remain incompletely understood [15].

Experimental and translational research has demonstrated that hydrogen sulfide is endogenously produced in response to physiological stressors, including mechanical load and metabolic demand. Preclinical studies indicate that physical exercise upregulates hydrogen sulfide–producing enzymes and enhances H_2S bioavailability in skeletal muscle and vascular tissue. These findings suggest that hydrogen sulfide participates in exercise-induced adaptive signaling pathways [16].

Despite these advances, clinical evidence linking hydrogen sulfide biosignaling to functional outcomes in rehabilitation settings is limited. Most available data are derived from animal models or in vitro systems, while human studies remain scarce and primarily indirect [17]. Furthermore, although sulfurous balneotherapy is widely applied in PRM, its interaction with exercise-induced endogenous hydrogen sulfide signaling has not been systematically investigated. The absence of integrated clinical and biological studies represents a critical knowledge gap that limits the mechanistic interpretation of rehabilitation outcomes and the optimization of multimodal interventions [18].

At physiological concentrations, hydrogen sulfide exerts its biosignaling effects primarily through redox-sensitive mechanisms, including post-translational modification of cysteine residues (persulfidation), modulation of mitochondrial electron transport, and regulation of transcription factors involved in cellular stress responses. These mechanisms overlap substantially with those activated by physical exercise, such as AMP-activated protein kinase, nuclear factor erythroid 2–related factor 2, and sirtuin-dependent pathways [19].

Exercise-induced reactive oxygen species production functions as a signaling event that drives adaptive responses rather than as a purely damaging process [20]. Hydrogen sulfide plays a modulatory role in this context, fine-tuning redox signaling and protecting cellular structures from excessive oxidative damage [21,22]. In rehabilitation populations characterized by chronic low-grade inflammation and oxidative stress, hydrogen sulfide–mediated signaling may enhance the efficiency of exercise-induced adaptation and support functional recovery [23,24].

Exogenous hydrogen sulfide exposure through sulfurous balneotherapy may further modulate these pathways within a hormetic framework, augmenting endogenous biosignaling rather than replacing it. This biological interaction provides a mechanistic rationale for combining therapeutic exercise with sulfurous balneotherapy in rehabilitation programs [25].

Understanding hydrogen sulfide as a biosignal in exercise-induced adaptation has direct implications for PRM and balneology. It provides a biological framework for interpreting the clinical effects of sulfurous balneotherapy and supports integrating molecular signaling concepts into rehabilitation practice.

By elucidating the mechanisms through which physical exercise and balneotherapy interact, this research may contribute to the development of biologically informed, personalized rehabilitation protocols that optimize functional outcomes while minimizing adverse effects.

The primary objective of this study is to evaluate the role of exercise-induced hydrogen sulfide–related biosignaling in functional adaptation during a structured rehabilitation program in patients with chronic musculoskeletal disorders.

The secondary objectives are: to determine whether the addition of sulfurous balneotherapy to therapeutic exercise enhances functional outcomes compared with exercise alone; to assess changes in systemic biomarkers of oxidative stress and inflammation as surrogate indicators of hydrogen sulfide–dependent biosignaling; to explore associations between biological markers and functional performance measures. Exploratory objectives include examining the feasibility of using redox- and inflammation-related biomarkers to reflect hydrogen sulfide signaling in a clinical rehabilitation setting indirectly and to inform future mechanistic studies.

Primary Hypothesis. Therapeutic exercise induces functional adaptation by activating hydrogen sulfide–related biosignaling pathways, as reflected in improvements in functional outcomes and modulation of systemic biomarkers.

Secondary Hypotheses. The combination of therapeutic exercise and sulfurous balneotherapy will result in greater functional improvements compared with therapeutic exercise alone. Combined intervention will lead to more pronounced reductions in oxidative stress and inflammatory biomarkers. Changes in biological markers will correlate with improvements in functional performance and pain-related outcomes.

2. Materials and Methods

The study is designed as a prospective, controlled, parallel-group clinical trial to be conducted in a balneological rehabilitation setting. The primary purpose of the protocol is to investigate exercise-induced hydrogen sulfide–related biosignaling and its association with functional adaptation, with particular emphasis on the modulatory role of sulfurous balneotherapy as an adjunct to therapeutic exercise.

The intervention period is planned to span 14 consecutive days, corresponding to a standard rehabilitation cycle commonly applied in balneological practice. Study assessments will be performed at baseline (T0), before the initiation of the intervention, and at the end of the intervention period (T1), allowing evaluation of short-term functional and biological responses to the planned interventions.

The study will be conducted in a certified balneological rehabilitation center equipped with dedicated facilities for supervised therapeutic exercise and sulfurous mineral water treatments. The sulfurous mineral water used for balneotherapy will be characterized before study initiation through physicochemical analyses, including hydrogen sulfide concentration, mineral composition, and temperature stability. These analyses will be performed in accordance with national and international balneological standards to ensure consistency, safety, and reproducibility of exposure.

Eligible participants will be adults aged 40–70 years with a clinical diagnosis of chronic musculoskeletal disorders, including knee or hip osteoarthritis or chronic non-specific low back pain, established according to recognized diagnostic criteria. Participants must have experienced persistent symptoms for at least 6 months and demonstrate sufficient functional capacity to participate in a supervised therapeutic exercise program. The ability and willingness to provide written informed consent will be mandatory for inclusion.

Exclusion criteria will include inflammatory rheumatic diseases or acute musculoskeletal conditions, severe cardiovascular, respiratory, neurological, or metabolic disorders that contraindicate exercise or balneotherapy, active systemic inflammatory or infectious diseases, recent surgical interventions or intra-articular injections within the preceding three months, current use of high-dose antioxidant or anti-inflammatory supplementation, and known contraindications to sulfurous balneotherapy.

A target sample size of approximately 60 participants is planned, based on feasibility considerations and effect sizes reported in previous rehabilitation and balneotherapy studies. Participants will be allocated into two groups: an Exercise Group (EG), receiving therapeutic exercise alone, and an Exercise plus Balneotherapy Group (EBG), receiving therapeutic exercise combined with sulfurous balneotherapy.

Group allocation will be performed using a controlled randomized procedure to ensure baseline comparability between groups with respect to age, sex, clinical diagnosis, and baseline functional status.

All participants will undergo a standardized, supervised therapeutic exercise program designed in accordance with current Physical and Rehabilitation Medicine guidelines and adapted to chronic musculoskeletal conditions. The program will include moderate-intensity aerobic exercise, such as walking or cycle ergometry performed at 50–65% of age-predicted maximal heart rate, progressive resistance exercises targeting major muscle groups relevant to the affected anatomical region, mobility and flexibility exercises focusing on joint range of motion, and functional and postural training aimed at improving balance, coordination, and movement efficiency.

Each exercise session will last approximately 45 minutes and will be conducted five days per week throughout the 14-day intervention period. Exercise intensity and progression will be individually adjusted based on baseline functional assessment and clinical tolerance under the supervision of trained physiotherapists.

Participants allocated to the EBG will additionally receive sulfurous balneotherapy administered according to standardized balneological protocols. Balneotherapy sessions will be conducted using sulfurous mineral water with documented hydrogen sulfide content, maintained at 36–38°C. Each session will last approximately 20 minutes and will be performed once daily, 5 days per week, for a total of 10–12 sessions over the intervention period.

Hydrogen sulfide exposure will occur primarily through cutaneous absorption and inhalation of water vapor. All sessions will be supervised by trained balneology personnel, and participant tolerance and safety will be monitored throughout the intervention.

Participants in the comparator group will receive therapeutic exercise alone, following the same exercise protocol, frequency, and duration as the experimental group. No balneotherapy will be administered. Standard rehabilitation care consistent with routine PRM practice will be provided.

A sham balneotherapy intervention will not be implemented due to feasibility constraints and the distinctive sensory characteristics of sulfurous mineral water. This limitation will be taken into account in the interpretation of the study's findings.

Exercise session attendance will be recorded daily, and balneotherapy attendance will be documented by clinical staff. Participants missing more than 20% of scheduled sessions will be considered non-compliant for per-protocol analyses.

Intervention fidelity will be ensured through standardized written protocols for exercise and balneotherapy, delivery by trained personnel, predefined parameters for temperature, duration, and safety, and regular team meetings to ensure consistency across participants.

The primary outcome will be the change in functional capacity from baseline (T0) to post-intervention (T1), assessed using the Six-Minute Walk Test (6MWT), a

validated and clinically meaningful measure of submaximal functional performance in rehabilitation populations.

Secondary functional outcomes will include the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and additional objective mobility and performance measures relevant to the target condition. Patient-reported outcomes will consist of pain intensity assessed using the Visual Analog Scale (VAS) and self-reported functional limitations and well-being.

Secondary biological outcomes will include markers of oxidative stress, such as malondialdehyde (MDA) and total antioxidant capacity (TAC), and markers of inflammation, including C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α). All secondary outcomes will be assessed at T0 and T1.

Exploratory outcomes will include analyses of correlations between functional improvements and biological markers, assessment of the feasibility of using redox- and inflammation-related biomarkers as indirect indicators of hydrogen sulfide–related biosignaling, and preliminary mechanistic insights into exercise–balneotherapy interactions.

Data analysis will be performed using standard statistical software. Continuous variables will be expressed as mean ± standard deviation or as median with interquartile range, as appropriate. Baseline characteristics will be summarized using descriptive statistics. Between-group comparisons will be conducted using parametric or nonparametric tests, as applicable, while within-group changes will be assessed using paired tests. Repeated-measures analyses will be applied to evaluate time-by-group interactions. Missing data will be addressed using appropriate imputation methods or sensitivity analyses. Exploratory subgroup analyses may be conducted based on diagnosis or baseline functional status. A two-sided p-value of less than 0.05 will be considered statistically significant.

Participants will be monitored daily for adverse events related to therapeutic exercise or balneotherapy. Adverse events will be defined as any unfavorable medical occurrence during the intervention period and will be documented and reported in accordance with institutional guidelines. The study may be terminated prematurely if unexpected serious adverse events related to the intervention occur.

3. Ethical Considerations

The study protocol will be reviewed and approved by an institutional ethics committee before initiation. All procedures will adhere to the principles of the Declaration of Helsinki. Written informed consent will be obtained from all participants before enrollment. Participants will be informed of their right to withdraw at any time without affecting their standard of care.

4. Strengths and Limitations

A key strength of this study protocol is its integrative, biologically informed design, which combines functional rehabilitation outcomes with biological markers reflecting hydrogen sulfide–related biosignaling. This approach addresses a crucial translational gap between molecular signaling research and clinical practice in physical and rehabilitation medicine.

The protocol incorporates a standardized and supervised therapeutic exercise program, ensuring intervention consistency and clinical relevance. The inclusion of sulfurous balneotherapy, delivered in accordance with established balneological standards, enhances the ecological validity of the study and reflects real-world rehabilitation practice.

The use of validated functional outcome measures and widely accepted biomarkers of oxidative stress and inflammation strengthens the reliability and comparability of the findings. Blinded outcome assessment and predefined statistical analysis procedures further contribute to methodological rigor and reduce the risk of measurement and analytical bias.

Finally, the prospective, controlled design and clearly defined eligibility criteria support internal validity and reproducibility, providing a robust framework for future confirmatory trials.

Several limitations are anticipated. First, because of the nature of the interventions, blinding participants and therapists is not feasible, which may introduce performance bias. Second, the relatively short intervention duration may limit the ability to detect long-term functional and biological adaptations. Third, the study relies on indirect biomarkers of hydrogen sulfide biosignaling rather than direct measurement of circulating or tissue H_2S levels, which may constrain mechanistic interpretation.

Additionally, the planned sample size, while appropriate for an exploratory controlled trial, may limit statistical power for subgroup analyses and reduce generalizability beyond the selected patient population and rehabilitation setting.

To mitigate potential biases, several methodological safeguards are incorporated into the protocol. Outcome assessors and data analysts will be blinded to group allocation, reducing detection and analysis bias. Standardized intervention protocols, delivered by trained personnel, will minimize variability in treatment delivery and enhance intervention fidelity.

Objective functional tests will be prioritized alongside patient-reported outcomes to reduce reliance on subjective measures. Predefined inclusion and exclusion criteria, along with a detailed statistical analysis plan, will limit selection bias and analytical bias. Compliance monitoring and documentation of adherence will further support the validity of per-protocol and intention-to-treat analyses.

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