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MINIREVIEWS

Molecular hydrogen therapy in musculoskeletal conditions: An evidence-based review and critical analysis

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Abstract

Molecular hydrogen (H_2) demonstrates selective antioxidant and anti-inflammatory properties with therapeutic potential across musculoskeletal conditions including osteoarthritis, rheumatoid arthritis, exercise-induced muscle damage, chronic pain syndromes, tendinopathies, and muscle atrophy. This review critically evaluates preclinical and clinical evidence for H_2 therapy and identifies research gaps. A comprehensive search of PubMed, EMBASE, and Cochrane Library (up to April 2025) yielded 45 eligible studies: 25 preclinical and 20 clinical trials. Preclinical models consistently showed reductions in reactive oxygen species, inflammatory cytokines, and improved cell viability. Clinical trials reported symptomatic relief in osteoarthritis, decreased Disease Activity Score 28 in rheumatoid arthritis, and accelerated clearance of muscle damage markers. Delivery methods varied - hydrogen-rich water, gas inhalation, and saline infusion - hindering direct comparison. Mechanistic biomarkers were inconsistently re-

ported, limiting understanding of target engagement. Common limitations included small sample sizes, short durations, and protocol heterogeneity. Despite these constraints, findings suggest H_2 may serve as a promising adjunctive therapy *via* antioxidant, anti-inflammatory, and cytoprotective mechanisms. Future research should prioritize standardized delivery protocols, robust mechanistic endpoints, and longer-term randomized trials to validate clinical efficacy and optimize therapeutic strategies.

Key Words: Molecular hydrogen; Musculoskeletal disorders; Oxidative stress; Anti-inflammation; Clinical evidence

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Core Tip: Molecular hydrogen therapy exhibits potent antioxidant, anti-inflammatory, and cytoprotective effects across diverse musculoskeletal conditions. This review synthesizes evidence from 45 studies - spanning osteoarthritis, rheumatoid arthritis, muscle damage, chronic pain, and atrophy - highlighting promising symptomatic relief and mechanistic plausibility. However, variability in delivery methods, sample sizes, and endpoints demands standardized trials with biomarker-driven designs to validate molecular hydrogen's efficacy and guide clinical integration.

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INTRODUCTION

Molecular hydrogen (H_2), long regarded as biologically inert, has recently emerged as a potent therapeutic agent in biomedicine[1,2]. Over the past decade, an expanding body of literature has demonstrated its diverse physiological effects, underscoring its therapeutic promise across a wide range of medical conditions[3]. Central to its proposed mechanism is its selective antioxidant activity, whereby it neutralizes highly reactive and cytotoxic radicals such as hydroxyl and peroxynitrite, while sparing crucial signaling species like superoxide and nitric oxide[4]. This specificity in radical scavenging is considered essential to its protective effects[5]. Beyond antioxidation, H_2 exerts anti-inflammatory, antiapoptotic, and immunomodulatory actions[6]. Additionally, it influences energy metabolism, modulates cellular signaling cascades, and alters gene expression[5]. Its small molecular size and high infusibility enable rapid penetration of biological membranes, allowing systemic distribution, including to central nervous system tissues. H_2's excellent safety profile is well-documented in clinical studies; it has not shown toxicity even at high concentrations and holds "generally recognized as safe" status from the Food and Drug Administration[7]. H_2 is the smallest and lightest molecule in the universe, consisting of two hydrogen atoms covalently bonded. With a molecular weight of 2.02 g/mol and high diffusion coefficient, H_2 readily crosses biological membranes including the blood-brain barrier. Its neutral charge and lipophilic properties enable rapid equilibration across cellular compartments within minutes of administration.

Musculoskeletal (MSK) disorders encompass a diverse array of conditions involving muscles, bones, joints, tendons, ligaments, and peripheral nerves. They are a leading cause of chronic pain and disability worldwide, imposing a profound burden on quality of life. Current treatments for musculoskeletal conditions often fall short, offering limited disease-modifying capacity and only partial symptomatic relief, which are frequently associated with side effects that restrict their long-term use. H_2's antioxidant and anti-inflammatory mechanisms align closely with the pathophysiological processes to musculoskeletal disorders, providing a strong rationale for its therapeutic application[3]. Its ability to selectively neutralize harmful radicals and modulate inflammation at the cellular level may allow for targeted intervention in both acute and chronic musculoskeletal pathologies[6,7]. The consistent observation of its broad-spectrum effects ranging from osteoarthritis to muscle atrophy, suggests that H_2 may act on shared pathological pathways, such as oxidative stress and inflammation, thereby offering wide clinical applicability[8,9]. The favorable safety profile of H_2, in contrast with the side effects of conventional pharmacological therapies, reinforces its suitability for long-term use. Its minimal toxicity and regulatory approval for safety enhance its translational potential, especially in chronic conditions requiring sustained management. This combination of efficacy and safety positions H_2 as a promising adjunctive or even foundational therapy for a broad spectrum of musculoskeletal conditions. This review examines the preclinical and clinical evidence for H_2 therapy across major musculoskeletal conditions, analyzes molecular mechanisms of action, evaluates delivery methods and safety profiles, identifies current limitations, and proposes directions for future research to advance clinical translation.

LITERATURE REVIEW

A systematic search was performed in PubMed, Scopus, EMBASE, Web of Science and the Cochrane Library from

database inception through April 2025. Search strategies employed the following Boolean operators: ("molecular hydrogen" OR "hydrogen gas" OR "hydrogen therapy" OR "H_2 therapy") AND ("musculoskeletal" OR "osteoarthritis" OR "rheumatoid arthritis" OR "muscle damage" OR "tendinopathy" OR "muscle atrophy" OR "fibromyalgia" OR "chronic pain") AND ("randomized controlled trial" OR "clinical trial" OR "preclinical" OR "in vitro" OR "animal model"). Search terms were adapted for each database's controlled vocabulary. Eligible studies were original research articles published in English that investigated hydrogen interventions in the context of musculoskeletal outcomes. These included *in vitro* assays, animal models, and clinical trials, provided they reported relevant quantitative data. Studies were selected based on their focus on hydrogen application for musculoskeletal conditions, encompassing a range of experimental designs across human, animal, and cellular systems. Studies were excluded if they were review articles, editorials, or conference abstracts lacking full texts. Non-English publications were also excluded, along with studies that did not involve hydrogen interventions or failed to report sufficient outcome data. Duplicate publications were removed to ensure the integrity of the dataset.

Two reviewers independently screened titles and abstracts. Full-text articles of potentially relevant studies underwent detailed evaluation. Discrepancies were resolved by consensus or consultation with a third reviewer. Extracted data included study design, participant or animal model characteristics, intervention details (mode, dose, duration), outcome measures (biochemical markers, functional tests, patient-reported symptoms) and mechanistic insights. Risk of bias for clinical trials was assessed using the Cochrane Collaboration's tool; animal studies were appraised with the Systematic Review Center for Laboratory animal Experimentation risk of bias tool. A narrative synthesis was organized by musculoskeletal condition, noting effect sizes and statistical significance where available. Heterogeneity in interventions and outcome measures was documented. Critical appraisal focused on sample size, blinding procedures, control conditions and consistency of mechanistic endpoints to inform future trial design.

The heterogeneity in intervention modalities, dosing regimens, and outcome measures significantly compromises the validity of pooled effect estimates. The small sample sizes (median n = 30) and short intervention periods (median 4 weeks) contribute directly to the predominantly "low" or "very low" Grading of Recommendations Assessment, Development and Evaluation evidence ratings observed across studies. Specifically, imprecision due to small samples reduces confidence in effect estimates, while inconsistent dosing protocols introduce methodological heterogeneity that precludes reliable meta-analysis. The brief intervention periods may be insufficient to detect clinically meaningful changes in chronic musculoskeletal conditions, particularly for structural outcomes like cartilage preservation or joint space narrowing.

MOLECULAR MECHANISMS OF HYDROGEN IN MUSCULOSKELETAL HEALTH

The therapeutic effects of H_2 in musculoskeletal conditions are underpinned by a multifaceted array of molecular mechanisms, primarily revolving around its capacity to modulate cellular redox homeostasis, inflammatory cascades, and cell survival pathways.

Antioxidant properties: Selective scavenging of hydroxyl radicals and peroxynitrite

H_2 functions as a potent and selective antioxidant[10,11]. Its unique selectivity lies in its ability to target the most detrimental reactive oxygen species (ROS), specifically the hydroxyl radical, and reactive nitrogen species such as peroxynitrite. Unlike many conventional antioxidants, H_2 does not neutralize beneficial signaling molecules like superoxide or nitric oxide, which are crucial for maintaining normal physiological functions[12]. This selective action minimizes potential disruption of vital cellular signaling pathways, ensuring that essential physiological processes remain unaffected. The reaction of H_2 with hydroxyl radicals result in the formation of water, thereby effectively preventing further free radical-induced damage[13]. Similarly, its interaction with peroxynitrite leads to the formation of nitrite and water, neutralizing this highly reactive nitrogen species[14].

Oxidative stress, characterized by an imbalance between the production of ROS and the body's antioxidant defenses, is a critical pathological contributor to various musculoskeletal conditions. This imbalance leads to cellular damage, lipid peroxidation, and mitochondrial dysfunction. In conditions such as rheumatoid arthritis, ROS play a central role in disease pathogenesis by amplifying inflammatory responses and directly degrading joint components, including collagen and hyaluronic acid[12]. H_2's capacity to mitigate this oxidative damage is therefore considered a primary mechanism underpinning its therapeutic effects in musculoskeletal disorders.

Anti-inflammatory effects: Modulation of signaling pathways

Beyond its antioxidant role, H_2 exhibits significant anti-inflammatory properties[12]. Its anti-inflammatory action is primarily mediated by inhibiting the secretion of proinflammatory factors and the activation of key proinflammatory signaling pathway[15,16]. In the context of rheumatoid arthritis, H_2 has the potential to disrupt detrimental positive feedback loops involving nuclear factor-kappa B (NF-κB) and tumor necrosis factor (TNF)-α[17-20]. NF-κB is a pivotal transcription factor that orchestrates the induction of various pro-inflammatory cytokines, including TNF-α, interleukin (IL)-1, and IL-6. TNF-α, in turn, can reactivate NF-κB, creating a self-perpetuating cycle of inflammation. By scavenging hydroxyl radicals, H_2 can effectively break down this "ROS-NF-κB-TNF-α redox sensing loop," thereby reducing inflammation-mediated tissue damage[21].

Clinical and preclinical investigations support these anti-inflammatory actions. Studies have demonstrated that H_2 reduces exercise-induced pro-inflammatory responses and oxidative stress[22]. In a mouse model of muscle atrophy, hydrogen-rich water (HRW) treatment significantly reduced skeletal muscle tissue levels of inflammatory markers such

as IL-6 and TNF-α[23]. Similarly, a pilot study in rheumatoid arthritis patients showed that H_2-saline infusion significantly decreased IL-6 levels[18]. Inflammation is a critical component of most musculoskeletal conditions, contributing to pain, tissue damage, and functional impairment[24]. Through the modulation of these inflammatory cascades, H_2 offers a pathway to alleviate symptoms and potentially slow disease progression.

The translational roadblock of hydrogen therapy for musculoskeletal disorders

Despite robust preclinical evidence demonstrating hydrogen's antioxidant and anti-inflammatory properties, its translation to human musculoskeletal conditions has yielded inconsistent results. Several factors may help explain this gap between laboratory findings and clinical outcomes. One key issue is species-specific differences in bioavailability. Human tissue distribution and the half-life of hydrogen may differ substantially from those observed in rodent models. While animal studies suggest rapid tissue penetration, pharmacokinetic data in humans remain limited, which could account for the discrepancy between preclinical efficacy and clinical uncertainty. Another challenge lies in the limitations of disease modeling. Preclinical models of osteoarthritis and rheumatoid arthritis often rely on acute injury or chemical induction, approaches that may not accurately reflect the complex and chronic inflammatory environment of human disease. The multifactorial nature of musculoskeletal pathology in humans including genetic predisposition, environmental influences, and age-related degeneration is not adequately captured in current animal models. Dosing and exposure considerations further complicate the translation. Effective doses in preclinical studies may not correspond directly to human-equivalent doses due to differences in metabolic rate, body composition, and hydrogen clearance mechanisms. The optimal therapeutic window for hydrogen in human subjects remains undefined, leaving a critical gap in our understanding of its clinical potential.

Antiapoptotic and cell protective effects

H_2 has been identified for its antiapoptotic properties[25]. It contributes to cellular resilience by protecting against various forms of cellular stresses that can lead to premature apoptosis[26]. In the context of osteoarthritis, cell and animal studies provide evidence that HRW or hydrogen-releasing hydrogels effectively mitigate osteoarthritis-induced cartilage damage, promote cartilage regeneration, and inhibit chondrocyte apoptosis[24]. This protective effect on chondrocytes is vital for preserving joint health and function[27]. Apoptosis, or programmed cell death, plays a significant role in the degeneration of tissues observed in musculoskeletal conditions, such as cartilage degradation in osteoarthritis[28]. Therefore, protecting cells from premature death is crucial for maintaining tissue integrity and facilitating repair processes.

Influence on energy metabolism and mitochondrial function

H_2's therapeutic scope extends to the regulation of energy metabolism[1]. It has been shown to improve mitochondrial function, which is particularly relevant given that mitochondria are primary sites of ROS production and their dysfunction contributes to oxidative stress and fatigue in conditions like fibromyalgia and muscle atrophy[26]. H_2 is hypothesized to alleviate the reduction in adenosine triphosphate generation caused by mitochondrial damage, potentially by forming a hydrogen ion gradient independent of the mitochondrial electron transport chain[26]. It also contributes to reducing mitochondrial oxidative stress and inflammation[23]. Impaired energy metabolism and mitochondrial dysfunction are implicated in muscle fatigue, chronic pain, and muscle wasting[23]. By supporting mitochondrial health, H_2 could address fundamental energetic deficits within affected musculoskeletal tissues.

Modulation of gene expression and cell signaling

H_2's influence extends to modulating signal transduction and gene expression[1]. A notable mechanism involves the activation of the nuclear factor erythroid 2-related factor 2 (Nrf2)/Kelch-like ECH associated protein 1 signaling pathway, a critical regulator for enhancing endogenous antioxidant enzymes and orchestrating the transcription of over 200 cytoprotective genes[23]. This pathway plays a role in detoxification, antioxidation (*e.g.*, NAD(P)H:quinone oxidoreductase 1, NAD(P)H:quinone oxidoreductase 2, heme oxygenase-1), antiapoptosis (*e.g.*, B-cell lymphoma 2), and metabolic processes[29]. In osteoarthritis, the observed benefits are likely associated with the suppression of the c-Jun N-terminal kinase (JNK) signaling pathway and the downregulation of wingless/integrated/β-catenin activation in chondrocytes[24]. H_2 has been shown to suppress apoptosis and inflammation in chondrocytes through the JNK pathway [28]. These signaling pathways are central to cellular responses to stress, inflammation, and damage, indicating that H_2's modulation of these pathways suggests a sophisticated level of biological interaction beyond simple free radical scavenging.

Potential role in pain modulation

H_2 has demonstrated potential in addressing chronic pain syndromes, including neuropathic pain and fibromyalgia[30]. Animal models of neuropathic pain (*e.g.*, rats with sciatic nerve injury) have shown that drinking HRW can relieve symptoms such as mechanical allodynia and thermal hyperalgesia[30]. This analgesic effect is linked to a reduction in oxidative stress within the spinal cord and dorsal root ganglia[30,31]. H_2 is reported to possess analgesic, anti-inflammatory, anxiolytic, and antidepressant properties, which are highly relevant given the frequent psychological comorbidities associated with chronic pain[30,31]. For fibromyalgia, H_2 is believed to reduce hyperalgesia by modulating pain pathways, improve fatigue, and offer anxiolytic effects[32]. It also contributes to mitochondrial protection by reducing oxidative stress, a common impairment in fibromyalgia patients[32,33]. While direct evidence for H_2's modulation of specific pain-related ion channels like transient receptor potential channels is not explicitly detailed, these channels are known molecular sensors for noxious stimuli and are involved in nociception and neuroinflammation[34].

Given H_2's broad effects on inflammation and oxidative stress, future research may explore its indirect or direct modulation of these or other pain-related pathways. Chronic pain is a complex neurological disease involving persistent nociceptor and microglial overactivation, leading to oxidative stress, mitochondrial dysfunction, and neuroinflammation [35]. H_2's multifaceted actions on these underlying mechanisms suggest a promising role in pain management.

The various molecular mechanisms through which H_2 exerts its effects - antioxidation, anti-inflammation, antiapoptotic, metabolic regulation, and gene modulation - are not isolated but rather intricately interconnected. For instance, the reduction of oxidative stress directly contributes to decreased inflammation and improved mitochondrial function, which in turn protects against cellular apoptosis. This suggests a cascade of beneficial effects rather than single-point interventions. When H_2 scavenges reactive oxygen species, it directly impacts the initiation of inflammatory cascades and protects cellular powerhouses, the mitochondria. The activation of the Nrf2 pathway further enhances the body's own endogenous antioxidant and cytoprotective machinery, creating a positive feedback loop of cellular resilience. This interconnectedness implies that H_2 does not merely treat symptoms; it addresses fundamental cellular imbalances at multiple levels simultaneously. This "systems-level" modulation, rather than a single target effect, could explain its broad therapeutic potential across seemingly disparate conditions within the musculoskeletal system, potentially leading to more profound and sustained benefits than therapies targeting only one aspect of the pathology. This also suggests that future research should employ multi-omics approaches to fully unravel these complex interactions.

A particularly noteworthy aspect of H_2's mechanism is the activation of the Nrf2/Kelch-like ECH associated protein 1 pathway and the suggestion that H_2 may act as an "exercise mimetic due to its redox adaptogenic properties"[23]. This indicates that H_2's mechanism extends beyond direct scavenging of harmful radicals; it actively upregulates the body's intrinsic antioxidant and cytoprotective systems. The concept of an "exercise mimetic" implies that H_2 may induce beneficial cellular adaptations similar to those achieved through physical activity, which is a cornerstone of musculoskeletal health. This positions H_2 not merely as a supplement but as a potential "redox adaptogen" that enhances overall cellular resilience, as shown in Figures 1 and 2.

CLINICAL APPLICATIONS AND EVIDENCE IN SPECIFIC MUSCULOSKELETAL CONDITIONS

Exercise-induced muscle damage and recovery

Intense physical exertion leads to oxidative stress and inflammation, resulting in exercise-induced muscle damage, delayed onset muscle soreness, and reduced performance[22]. Traditional recovery strategies often fall short or have side effects[36]. H_2 therapy presents a promising alternative. A meta-analysis of 27 trials (597 participants) found no significant improvements in aerobic/anaerobic endurance or muscle strength, but H_2 significantly reduced perceived exertion (standardized mean difference = -0.37, P = 0.009) and improved lactate clearance (standardized mean difference = -0.37, P = 0.001)[36]. It also enhanced lower limb explosive power[36], suggesting its utility in recovery over performance enhancement. In a placebo-controlled crossover trial, 12 elite fin swimmers consumed HRW for 4 days. Post-exercise creatine kinase levels (P = 0.043), muscle soreness (Visual Analog Scale; P = 0.045), and countermovement jump height (P = 0.014) improved at 12 hours[22]. However, correlations among these markers weren't statistically significant[22], highlighting individual variability.

Osteoarthritis

Knee osteoarthritis (KOA) involves chronic inflammation and oxidative stress that degrade cartilage and impair joint function[24]. H_2 therapy has shown promise in modulating these pathological processes. Preclinical data reveal HRW and hydrogen hydrogels mitigate cartilage damage *via* suppression of JNK and wingless/integrated/β-catenin pathways, and reduce oxidative damage through peroxynitrite inhibition (Table 1)[24,27]. In Wang *et al*[24], 121 KOA patients received H_2-O_2 inhalation alongside a 12-week home exercise program. Western Ontario and McMaster Universities Arthritis Index scores improved significantly at week 2 (mean difference = -8.0, P = 0.024) but not at week 12 (P = 0.140), failing to meet the minimum clinically important difference. No differences were seen in inflammation markers or physical function tests. The short-term gains suggest dosage and duration are critical for sustained effects. H_2 may serve best as a symptom reliever or exercise enhancer rather than a standalone treatment[24]. Both groups benefited from exercise alone, implying H_2's synergistic potential. Larger trials are needed to verify long-term efficacy and uncover mechanistic pathways.

Rheumatoid arthritis and autoimmune conditions

Rheumatoid arthritis is a chronic autoimmune disease marked by joint destruction, systemic inflammation, and oxidative stress[37]. Molecular H_2 acts as a selective antioxidant, scavenging hydroxyl radicals and disrupting NF-κB and TNF-α feedback loops (Table 2)[12,37]. Ishibashi *et al*[18] showed that intravenous H_2-saline (1 ppm/day for 5 days) reduced Disease Activity Score 28 significantly from 5.18 ± 1.16 to 3.74 ± 1.22 after 4 weeks. IL-6 declined by 37%, matrix metalloproteinase-3 by 19%, and urinary 8- 8-hydroxy-2'-deoxyguanosine (8-OHdG) by 4.7%, while TNF-α remained unchanged. The placebo group showed no significant improvements. Another trial (NCT05196295) explored oral hydrogen-rich coral calcium in 15 autoimmune patients, including rheumatoid arthritis. Disease Activity Score 28 improved from 5.18 to 4.64 (P = 0.02) after 1 month, especially with higher doses. Brief Fatigue Inventory-Taiwan scores decreased significantly. Though C-reactive protein (CRP) and erythrocyte sedimentation rate trended down, changes weren't statistically significant[38]. A small open-label study reported reduced rheumatoid arthritis symptoms after HRW intake, though limited by size and controls[39]. Preclinical collagen-induced arthritis models support H_2's anti-inflammatory effects, showing reduced swelling, synovial hyperplasia, and cartilage damage[40]. Early-stage intervention might even prevent

Table 1 Clinical evidence of hydrogen therapy in osteoarthritis

Ref.	Year	Study design	Participants (number, characteristics, KL grade)	Intervention (method, dose, duration)	Primary outcome (WOMAC score, significance)	Secondary outcomes (inflammation, functional tests, QoL, significance)	Main conclusions (initial *vs* sustained effects)	Limitations
Wang *et al* [24]	2025	Open-label, blinded-endpoint, randomized controlled trial	121 elderly KOA patients (average age 812 years, 80.2% female; KL grade 2 or grade 3; KOA duration ≥ 6 months)	H_2-O_2 inhalation (2.0 L/minute H_2, 1.0 L/minute O_2) for 60 minute/day over 2 weeks, adjunctive to 12-week HBE program; control: HBE only	WOMAC total score: (1) Group H improved -22.9 from baseline ($P < 0.001$); (2) Group C improved -19.4 from baseline ($P < 0.001$); (3) Between-group difference at week-12: -5.2 ($P = 0.140$), not clinically significant (MCID = 9); and (4) Peak MD at week-2: -8.0 ($P = 0.024$)	(1) Inflammation (hs-CRP, NLR, PLR, LMR): No significant between-group differences at week-12 ($P > 0.4$); (2) Functional tests (CST, TUG): No significant between-group differences at week-12 ($P > 0.1$). Both groups improved from baseline; (3) QoL (SF-36): No significant between-group differences at week-12. Both groups improved from baseline; and (4) Adverse events: Low incidence, no significant difference	H_2-O_2 inhalation alleviated KOA symptoms and enhanced functional activity during initial 2 weeks. No sustained effects observed at 12 weeks	Open-label design (bias risk); self-reported adherence; no analysis of plasma inflammatory markers; control group did not receive O_2 inhalation; limited generalizability (CCRC population)

KL: Kellgren-Lawrence; KOA: Knee osteoarthritis; HBE: Home-based exercise; WOMAC: Western Ontario and McMaster Universities Arthritis Index; MCID: Minimum clinically important difference; MD: Mean difference; QoL: Quality of life; hs-CRP: High-sensitivity C-reactive protein; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; LMR: Lymphocyte-to-monocyte ratio; CST: Chair stand test; TUG: Timed up and go test; SF-36: Short Form 36 Health Survey Questionnaire; CCRC: Continuing care retirement community.

autoimmunity. Despite promising results, both studies were limited by small sample sizes, short duration, and lack of control groups[18,39]. Larger randomized controlled trials (RCTs) with precise biomarkers and stratified dosing are needed to validate H_2's potential as a targeted and possibly disease-modifying therapy in rheumatoid arthritis.

Chronic musculoskeletal pain syndromes

Chronic pain syndromes like neuropathic pain and fibromyalgia are complex conditions often linked to oxidative stress, neuroinflammation, and mitochondrial dysfunction (Table 3)[41,42]. Preclinical studies in rat models show that HRW alleviates neuropathic pain symptoms - such as allodynia and hyperalgesia - by reducing oxidative stress in the spinal cord and dorsal root ganglia[31]. Importantly, benefits were seen even when H_2 was administered during the induction phase, suggesting possible preventative effects. H_2 also shows anxiolytic and antidepressant properties, which may address the psychological comorbidities common in chronic pain[30]. This dual action encourages clinical trials measuring both pain relief and psychological outcomes, potentially reducing polypharmacy.

In fibromyalgia, H_2 may reduce hyperalgesia, fatigue, and oxidative damage[32,43]. A pilot study in chronic fatigue syndrome noted HRW's antioxidant benefit when paired with biofeedback[44]. Another trial on women with panic disorder reported improved body pain and physical health with HRW plus psychological therapy, despite non-significant group differences[45]. Despite promising preclinical and pilot findings, robust human trials remain scarce[35]. The exact molecular mechanisms - especially involving transient receptor potential channels - are still unclear[34]. Standardized protocols and biomarker-driven studies are needed to validate H_2's role in managing chronic musculoskeletal pain (Figure 3).

Tendinopathies and other soft tissue injuries

Tendinopathies and acute soft tissue injuries, including sprains and strains, are driven by inflammation and oxidative stress. Preclinical studies on rat Achilles tendons show HRW reduces tendon adhesion and inflammation *via* activation of the Nrf2 pathway, which modulates oxidative stress markers (*e.g.*, malondialdehyde, 8-OHdG) and boosts antioxidants like superoxide dismutase and glutathione (Table 4)[46]. Reducing tendon adhesions - a major postoperative complication - suggests H_2's potential as a disease-modifying therapy, improving recovery and function beyond symptom relief. It could benefit rehabilitation following surgery or severe tendon injuries by preventing motion-limiting adhesions. H_2 is also explored in athletic recovery. As an antioxidant and anti-inflammatory agent, it may reverse oxidative stress-induced damage and aid healing after intense training[22]. A small study involving 36 young men with soft tissue injuries found that oral and topical H_2 over 14 days improved joint flexibility and lowered plasma viscosity. However, inflammatory markers (CRP, IL-6) and clinical metrics (pain, swelling) were inconsistently affected. Despite promising preclinical evidence, translation to clinical practice remains limited. Challenges include poor face validity of models, inconsistent tendinopathy induction methods, and high bias risk[47].

Table 2 Clinical trials investigating hydrogen therapy in rheumatoid arthritis

Ref.	Year	Study design	Participants (number, conditions, characteristics)	Intervention (method, dose, duration)	Primary outcomes (measured)	Secondary outcomes (measured)	Statistical significance	Main conclusions	Limitations
Ishibashi *et al*[39]	2012	Small pilot study, open-label, no placebo control	20 RA patients	Hydrogen-rich water (duration 4 weeks)	Disease activity, oxidative stress markers	Significant decrease in disease activity and oxidative stress markers		Suggests potential benefits but requires further validation	Open-label, small sample size, lack of placebo control
Ishibashi *et al*[18]	2014	Randomized, double-blind, placebo-controlled pilot study	24 RA patients	Intravenous infusion of 500 mL of 1 ppm H_2-saline daily for 5 days	DAS28	IL-6, TNF-α, MMP-3, urinary 8-OHdG	DAS28: Significant decrease in H_2 group ($P < 0.05$); IL-6: Significant decrease in H_2 group ($P < 0.05$); MMP-3: Significant decrease in H_2 group ($P < 0.05$); 8-OHdG: Significant decrease in H_2 group ($P < 0.05$); TNF-α: No remarkable change	H_2 infusion safely and effectively reduced RA disease activity	Small sample size ($n = 24$); short duration (5-day infusion, 4-week follow-up); generalizability limited
Shen *et al* [38]	2022	Clinical trial (NCT05196295)	15 autoimmune patients (14 RA, 1 SLE; average age 54 years, 80% female)	Oral hydrogen-rich coral calcium: Low (1 capsule/day), medium (3 capsules/day), high (6 capsules/day) for 1 month	Safety (adverse effects)	DAS28, BFI-T, CRP, ESR, CBC, urinary biomarkers	Safety: No adverse effects reported; DAS28: Significant decrease overall ($P = 0.02$), pronounced in high dose ($P = 0.01$); BFI-T: Significant decrease overall ($P = 0.0002$), pronounced in high/medium doses; CRP/ESR: Trend of decrease, not statistically significant; WBC: Neutrophils: Significant decrease; monocytes: Significant increase	No adverse effects; potential therapeutic effects addressed for future studies	Small sample size ($n = 15$); short duration (1 month); no separate RA treatment control group; need for more calcium biomarkers; need for longer studies (≥3 months)

RA: Rheumatoid arthritis; SLE: Systemic lupus erythematosus; DAS28: Disease Activity Score 28; IL: Interleukin; TNF: Tumor necrosis factor; MMP-3: Matrix metalloproteinase-3; 8-OHdG: 8-hydroxy-2′-deoxyguanosine; BFI-T: Brief Fatigue Inventory-Taiwan; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; CBC: Complete blood count; WBC: White blood count.

Muscle atrophy

Muscle atrophy due to immobilization or disuse significantly impacts quality of life and increases morbidity[23]. Oxidative stress and inflammation are key contributors[23]. A preclinical mouse model (hind limb immobilization, $n = 36$) tested HRW and found notable improvements during both atrophy and recovery phases[23]. HRW enhanced muscle weight and limb grip strength, increased myofiber diameter, and reduced fibrosis[23]. It lowered serum troponin I and malondialdehyde levels, indicating reduced muscle damage and oxidative stress[23]. HRW also suppressed inflammatory markers (IL-6, TNF-α) and modulated apoptotic mediators, increasing NF-κB, Beclin 1, and Bax expression[23]. This suggests H_2 may actively prevent muscle loss during disuse and speed up post-atrophy recovery, offering a proactive therapy for immobilized patients - *e.g.*, post-surgical, intensive care unit-bound, or even astronauts. Unlike traditional interventions focused solely on recovery, H_2 could minimize atrophy severity and accelerate rehabilitation timelines. However, clinical research in humans is lacking[23]. Trials are needed to confirm its efficacy and clarify mechanisms involving inflammation, oxidative stress, and apoptosis modulation. H_2 may emerge as an adjunctive therapy to preserve muscle health and reduce long-term functional decline in immobilized populations.

Table 3 Overview of hydrogen therapy studies in chronic musculoskeletal pain

Ref.	Year	Condition	Study type	Participants/model (number, species)	Intervention (method, dose, duration)	Key outcomes (measured)	Observed effects/significance	Main conclusions	Limitations
Kawaguchi *et al*[31]	2014	Neuropathic Pain	Preclinical animal model	Rats (sciatic nerve injury model)	HRW ingestion (free access); also, during induction phase (day 0-4)	Mechanical allodynia, thermal hyperalgesia, oxidative stress markers (4-HNE, 8-OHdG) in spinal cord/DRG	HRW relieved allodynia and hyperalgesia; reduced oxidative stress in spinal cord/DRG. Effects observed even with short-term induction phase treatment	HRW may be beneficial for neuropathic pain	Preclinical (animal model); direct translation to humans needs validation
Ho *et al*[35]	2025	FM	Scoping review (preclinical and small-scale clinical)	Human FM patients, preclinical models	Redox-modulating therapies (include molecular hydrogen)	Pain, fatigue, sleep, oxidative stress markers (MDA, 4-HNE), mitochondrial dysfunction	Suggests potential benefits of molecular hydrogen; addresses oxidative stress and mitochondrial dysfunction	Human trial evidence is limited; standardized treatment protocols lacking	
Hirano *et al* [32]	2022	FM	Review/conceptual	FM patients	Hydrogen inhalers (daily 30 minutes - 1 hour)	Pain reduction (hyperalgesia), fatigue improvement, anxiolytic effect, mitochondrial protection	Hydrogen offers innovative approach for FM by neutralizing free radicals, reducing oxidative stress, modulating inflammation, and protecting mitochondria	Research still in early stages; further research needed (protocols, subgroups, long-term effects)	
Friedberg *et al*[44]	2025	Chronic fatigue syndrome (similar to FM)	Pilot randomized trial	13 participants (54% female, 46% male)	HRW + HRV-B	C19YRS-m, COMPASS-31, RMSSD, WHODAS, pain, fatigue, sleep, cognitive performance, inflammatory state	HRW has therapeutic antioxidant properties, beneficial in mitigating oxidative stress-induced damage *via* anti-inflammatory/anti-apoptotic pathways. Significant improvements in various patient profiles	Pilot study; small sample size (n = 13); primary focus on HRV-B; mechanisms need full explanation	
Fernández-Serrano *et al* [45]	2022	Panic disorder (with body pain)	Randomized, placebo-controlled clinical trial	Women with panic disorder	Psychological treatment + 1.5 L hydrogenated water for 3 months. Control: Psychological treatment + placebo	Severity of anxiety/depression, pro-inflammatory cytokine levels, cortisol awakening response, general health, body pain	Treatment group not significantly better overall, but further reduction in pro-inflammatory cytokine scores; improved body pain and physical health	Focus on panic disorder, not primary MSK pain; limited direct applicability to MSK pain syndromes	

FM: Fibromyalgia; HRW: Hydrogen-rich water; HRV-B: Human rhinovirus B; 4-HNE: 4-Hydroxynonenal; 8-OHdG: 8-hydroxy-2′-deoxyguanosine; DRG: Dorsal root ganglion; MDA: Malondialdehyde; C19YRS-m: Modified coronavirus disease 2019 Yorkshire Rehabilitation Scale; COMPASS-31: Composite Autonomic Symptom Score 31; RMSSD: Root mean square of successive difference; WHODAS: World Health Organization Disability Assessment Schedule; MSK: Musculoskeletal.

METHODS OF HYDROGEN ADMINISTRATION AND DOSAGES

H_2 exhibits excellent bioavailability and penetrates cellular barriers rapidly[13,48]. Its therapeutic effectiveness across tissues varies based on the delivery route chosen[3,49-53].

HRW

HRW remains a widely utilized approach, created either by pressurized H_2 infusion, electrolysis, or magnesium-based

Table 4 Preclinical and clinical findings on hydrogen therapy in tendinopathies and soft tissue injuries

Ref.	Year	Condition	Study type	Participants/model (number, species)	Intervention (method, dose, duration)	Key outcomes (measured)	Observed effects/significance	Main conclusions	Limitations
Meng *et al* [46]	2019	Tendon adhesion (post-repair)	Preclinical animal model	36 Sprague Dawley rats (tendon repair model)	Hydrogen water *vs* normal saline post-operative	Tendon adhesion, oxidative stress markers (MDA, 8-OHdG), antioxidant enzymes (SOD, GSH), Nrf2 pathway expression	HS group showed reduced tendon adhesion, lower MDA/8-OHdG, higher SOD/GSH. Associated with Nrf2 activation	Hydrogen water can reduce tendon adhesion and inhibit excessive inflammatory response, possibly *via* Nrf2 pathway	Preclinical (animal model); direct translation to humans needs validation
Sládečková *et al*[22]	2024	Muscle injury recovery	Review/conceptual	Athletes	Hydrogen therapy (drinking, bathing, inhaling)	Anti-oxidation, anti-inflammation, improved recovery from injury	Hydrogen therapy shows potential for muscle recovery by reducing oxidative stress and inflammation	Conceptual/review; lacks specific clinical trial data in these snippets	
Ostojic[3]	2016	Soft tissue injuries (sports-related)	Small-scale pilot clinical study	36 young men with sports-related soft tissue injuries	Oral and topical H_2 for 14 days, as complementary treatment	Joint flexibility, plasma viscosity, C-reactive protein, IL-6, pain scores, limb swelling	Faster return to normal joint flexibility; augmented plasma viscosity decrease. Other inflammation markers and clinical outcomes not consistently significant	Provides early support for H_2 in soft tissue injuries, but limited efficacy on general inflammation markers	Small sample size; short duration; pilot nature; inconsistent reporting of all outcomes
Agyeman-Prempeh *et al*[47]	2025	Tendinopathy (general preclinical)	Scoping review	Various animal models (*in vitro* & *in vivo*)	Various AT treatments (general)	Tendon properties (load, stiffness, fiber structure, collagen), inflammation	Promising preclinical outcomes (improved biomechanical, histological, biochemical properties)	Poor face validity of animal models; heterogeneity in AT induction; low quality/high risk of bias in included studies; translation to clinical practice lags	

AT: Achilles tendon; MDA: Malondialdehyde; 8-OHdG: 8-hydroxy-2′-deoxyguanosine; SOD: Superoxide dismutase; GSH: Glutathione; Nrf2: Nuclear factor erythroid 2-related factor 2; IL: Interleukin.

reactions[3]. It allows convenient, long-term intake. Human studies report ingestion volumes such as 1260-2520 mL/day at 0.9 ppm H_2 for muscle recovery[22], and 530 mL/day at 4-5 ppm for rheumatoid arthritis patients[3]. Animal models receive smaller amounts, *e.g.*, 15 mL/day with initial H_2 concentrations over 1.5 mmol/L, which remains above 0.1 mmol/L after 12 hours[23]. Its proven roles span neuromuscular recovery, inflammation, and pain[22].

Inhalation therapy

Hydrogen inhalation, typically under 4% H_2 concentration, utilizes specialized generators or nasal cannulas[3]. Oxygen balance is crucial[54]. This method targets pulmonary and cardiovascular systems but achieves systemic delivery *via* blood diffusion[54]. In KOA studies, subjects inhaled a H_2-O_2 mix (2.0 L/minute H_2, 1.0 L/minute O_2) for one hour daily for 2 weeks[24]. The route supports acute condition management like stroke, while its use in musculoskeletal disorders highlights its broad reach[54].

Intravascular saline injection

Sterile hydrogen-saturated saline provides rapid systemic distribution through intravenous infusion[55]. A preliminary rheumatoid arthritis trial delivered 500 mL of 1 ppm H_2-saline daily over five days[18]. This technique suits acute or

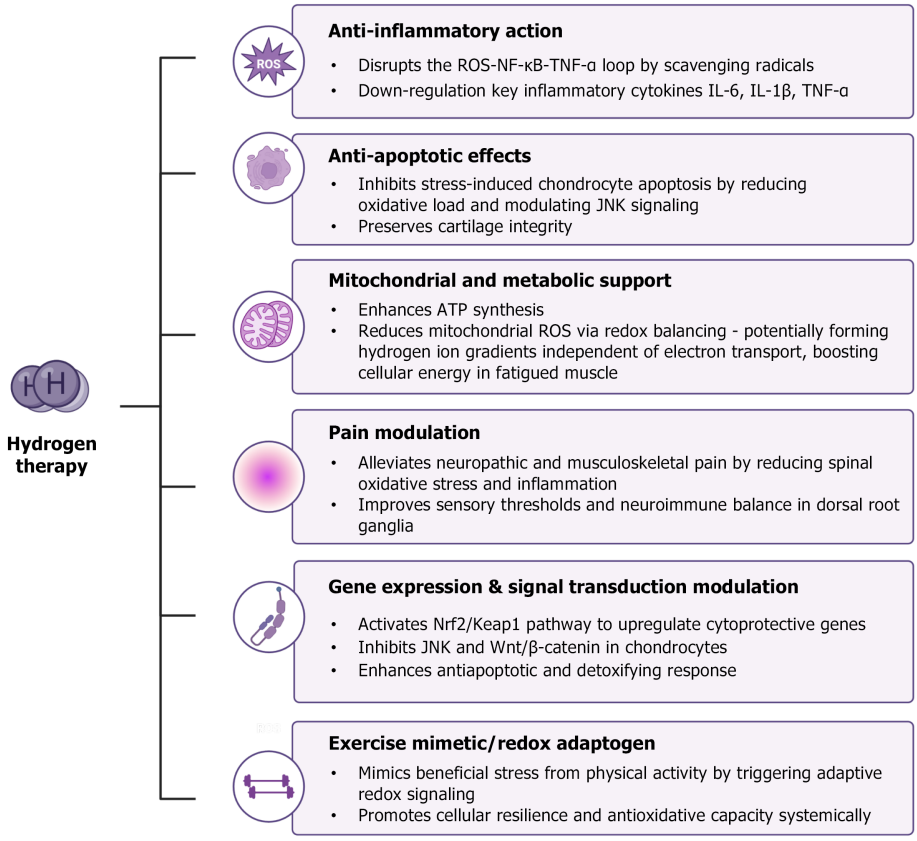


Figure 1 Molecular mechanisms of molecular hydrogen therapy in musculoskeletal ailments. ROS: Reactive oxygen species; NF-κB: Nuclear factor-kappa B; TNF: Tumor necrosis factor; IL: Interleukin; JNK: C-Jun N-terminal kinase; ATP: Adenosine triphosphate; Nrf2: Nuclear factor erythroid 2-related factor 2; Keap1: Kelch-like ECH-associated protein 1; Wnt: Wingless/integrated.

severe cases requiring immediate therapeutic intervention.

Topical administration

Localized application involves skin contact with hydrogen-enriched solutions[56]. Though less systemic, it serves soft tissue protocols well, often in tandem with oral H_2 administration[3]. Its utility appears promising for superficial musculoskeletal treatments.

Nanomedicine delivery systems

Emerging nanotechnology approaches for H_2 delivery include hydrogen-loaded nanoparticles[57-60], hydrogels[61-64], and microspheres that provide sustained release and targeted delivery[65,66]. These systems may overcome limitations of rapid H_2 diffusion and enable tissue-specific accumulation, potentially improving therapeutic efficacy while reducing dosing frequency.

Other methods

Alternative formats like oral capsules or tablets - *e.g.*, hydrogen-rich coral calcium - offer portability and controlled dosing [38]. However, efficacy relative to other routes is still under exploration.

TYPICAL CONCENTRATIONS AND DURATIONS

The optimal therapeutic dose for inhaled H_2 remains undefined. A proposed consumption dose is 80 mL hydrogen gas daily (6.6 mg or 3.3 mmol), with peak effects expected after one month[1,67]. However, significant variability in concentrations exists across research protocols and commercial products[3], underscoring the need for standardized dosing[36].

Efficacy appears highly dependent on dose, frequency, and duration. Transient improvements in KOA symptoms suggest short courses may be insufficient for chronic conditions[24], while rheumatoid arthritis studies highlight dose-dependent responses[68]. These inconsistencies reflect early-stage optimization challenges in H_2 therapy. To advance clinical translation, future studies must include pharmacokinetic and pharmacodynamic evaluations that define hydrogen's half-life, tissue retention, and molecular effects over time. Without such rigor, heterogeneous protocols will persist, hampering reliable efficacy assessments[36].

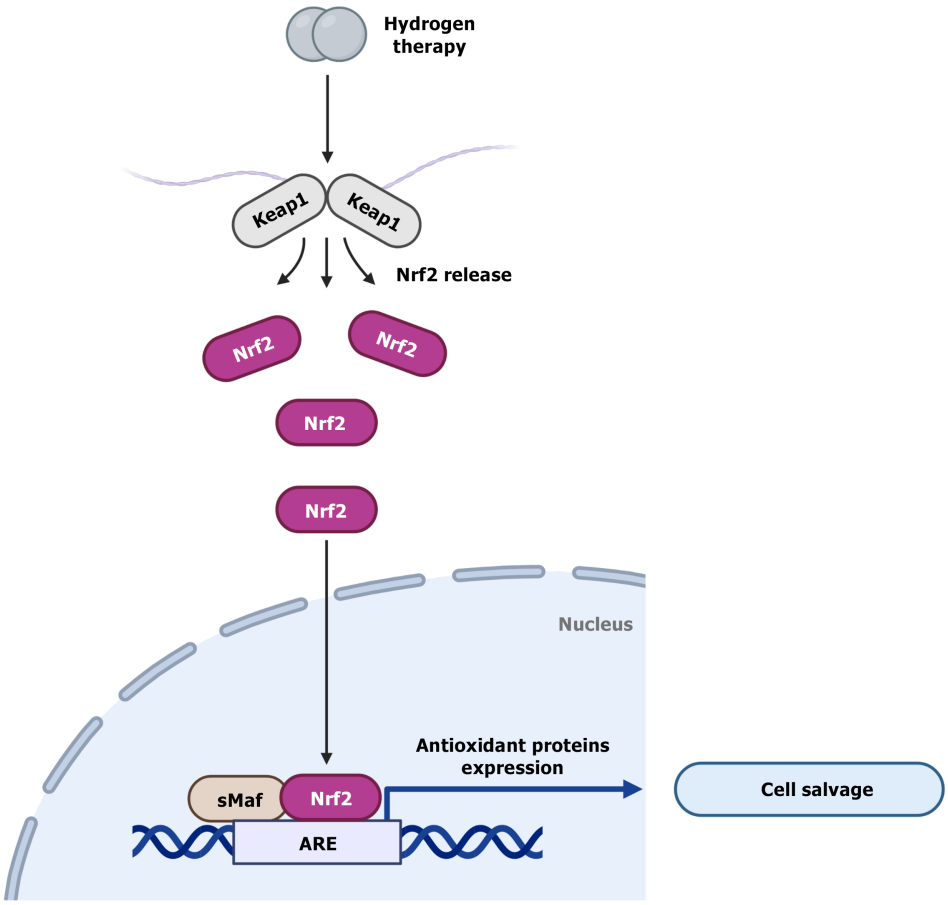


Figure 2 Molecular hydrogen -mediated nuclear factor erythroid 2-related factor 2/Kelch-like ECH associated protein 1 signaling pathway.
Keap1: Kelch-like ECH-associated protein 1; Nrf2: Nuclear factor erythroid 2-related factor 2; sMaf: Small Maf protein; ARE: Antioxidant response element.

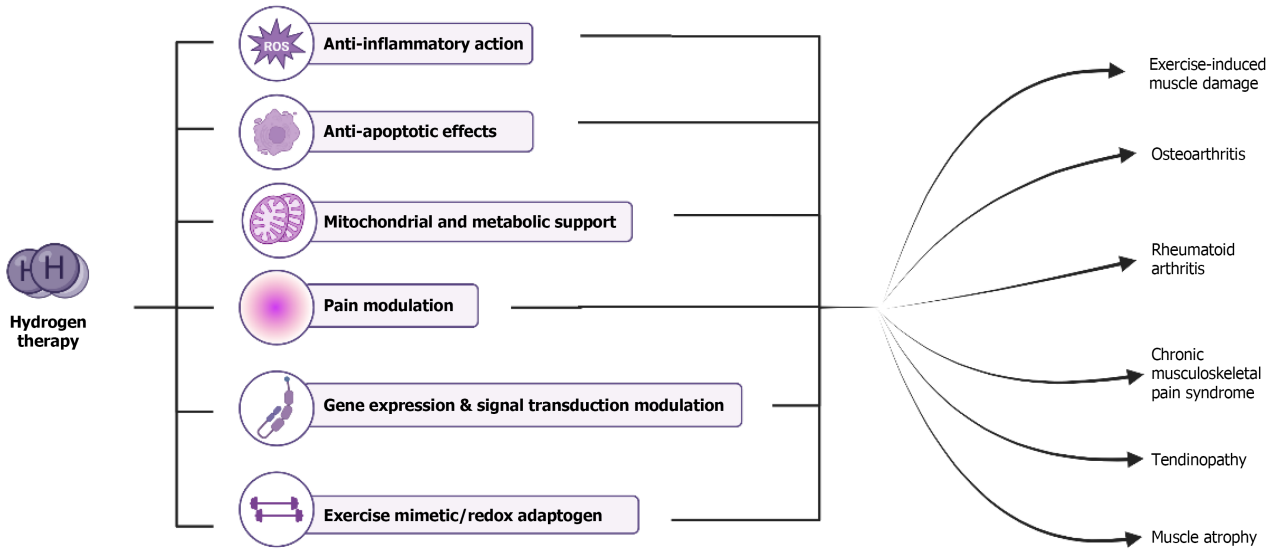


Figure 3 Molecular hydrogen therapy in musculoskeletal ailments.

Delivery method selection also plays a pivotal role. Each route offers distinct benefits, speeds, and tissue-specific actions. Systemic inflammatory diseases like rheumatoid arthritis may benefit more from intravenous or high-dose oral H_2, whereas localized conditions like KOA or tendinopathies could be treated with topical or inhalation therapies. This invites comparison across modalities and even combination approaches (*e.g.*, HRW + topical) to enhance efficacy and reduce overall dose. Ultimately, individualized dosing strategies and tailored delivery routes may be key to unlocking H_2's full therapeutic potential in musculoskeletal care (Table 5).

Table 5 Common hydrogen delivery methods and research dosages

Delivery method	Typical research dosages/concentrations	Administration duration	Targeted systems/conditions	Prospective	Disadvantages
hydrogen-rich water ingestion	0.9 ppm H_2 (1260 mL/day - 2520 mL/day) 4-5 ppm H_2 (530 mL/day) > 1.5 mmol/L H_2 (average 15 mL/day in mice) Proposed therapeutic dose: 80 mL H_2 gas (6.6 mg/3.3 mmol) per day	3 days to 4 weeks 1 month Up to 12 weeks	Muscle recovery; RA; neuropathic pain; muscle atrophy	Accessible; convenient for daily/Long-term use; systemic effects	H_2 can escape from containers; variability in commercial products
Hydrogen gas inhalation	< 4 % H_2 in air; 2.0 L/minute H_2 + 1.0 L/minute O_2 for 60 minutes	60 min/day over 2 weeks single sessions	Respiratory; cardiovascular; KOA; fibromyalgia; acute conditions (stroke)	Rapid systemic delivery; precise dosing with devices	Requires specialized equipment (inhaler/generator); risk if O_2 is insufficient or H_2 is contaminated
H_2-saturated saline injection	1 ppm H_2-saline (500 mL)	Daily for 5 days	RA; acute conditions (ischemic stroke)	Direct and rapid systemic delivery; bypasses GI tract	Invasive; requires medical professional administration
Topical application	Not specified (part of combined treatment)	Not specified (part of combined treatment)	Soft tissue injuries	Localized effect; potentially fewer systemic side effects	Limited systemic absorption; variable penetration
Oral tablets/capsules	Hydrogen-rich coral calcium: 170-1020 mg/day	1 month	Autoimmune diseases (RA, SLE)	Convenient; easy to administer	Absorption variability; potential for other ingredients (*e.g.*, calcium)

RA: Rheumatoid arthritis; KOA: Knee osteoarthritis; SLE: Systemic lupus erythematosus; GI: Gastrointestinal.

SAFETY PROFILE AND ADVERSE EFFECTS

H_2 holds a strong safety record, having been granted generally recognized as safe status by the United States Food and Drug Administration[7]. This designation affirms that H_2 is expected to be safe under its recommended usage guidelines. Historically, hydrogen's therapeutic use dates back to the late 1800, notably for detecting intestinal injuries[7]. Physically, H_2 gas is inert and remains non-flammable at concentrations below 4.7% in air[55]. Therapeutic applications typically use concentrations between 1%-4%, well below this flammability threshold[55].

A recurring theme across studies is the notable absence of serious adverse effects. Clinical trials consistently report H_2's tolerability across modalities. For instance: In the KOA study by Wang *et al*[24], the H_2-O_2 group experienced just three mild adverse events - two headaches and one nasal dryness - comprising 5% of participants. No statistically significant differences from the control group were noted. In the autoimmune study assessing hydrogen-rich coral calcium, no toxicity or adverse effects were reported over a month's administration. Participants even noted qualitative benefits in sleep, defecation, and energy levels[38].

Ishibashi *et al*[18] observed no adverse events in rheumatoid arthritis patients receiving intravenous H_2-saline. Reinforcing H_2's safety even in immune-compromised populations[55]. The fin swimmer trial demonstrated safe use of HRW during post-exercise recovery; no participants reported clinically meaningful negative responses[22]. This favorable safety profile is especially compelling for chronic musculoskeletal conditions, where patients often rely on non-steroidal anti-inflammatory drugs, corticosteroids, or biologics - each associated with considerable long-term risks. H_2's minimal toxicity positions it as an attractive adjunct or alternative therapy, particularly for elderly patients or those with polypharmacy concerns. Even with moderate efficacy, its positive risk-benefit ratio enhances patient adherence and expands potential clinical uptake.

However, while H_2 is inherently safe, administration technique matters. Excessive HRW intake, poor-quality inhalers, or inadequate oxygenation during H_2 inhalation can introduce risk[69,70]. Safety hinges on correct device use, purity assurance, and dosage control. Healthcare consultation is essential prior to initiating high-dose or prolonged H_2 protocols. H_2 also displays compatibility with other antioxidants and may complement pro-oxidant therapies without antagonistic effects, which enhances its versatility in multimodal treatments[71].

Critically, the safety conversation must expand beyond the molecular level to consider delivery systems (Table 6). Standards for HRW generators and inhalers must ensure contaminant-free H_2 and user-friendly operation. Clinical trial protocols should rigorously document H_2 source, purity, and delivery method, and differentiate adverse events attributable to H_2 itself *vs* device-related issues.

While H_2 is known for its excellent safety profile, the risks associated with specific delivery methods warrant careful attention. Inhalation devices, for instance, pose concerns related to oxygen displacement when hydrogen concentrations exceed 4% in confined spaces. If these devices are not properly maintained, they may deliver contaminated gas or

Table 6 Safety profile and reported adverse events of hydrogen therapy

Safety status	Observed adverse events (type, frequency, severity)	Associated delivery method	Context/condition of study	Important safety considerations
GRAS by FDA	No toxic side effects reported in many clinical trials	All methods (HRW, inhalation, injection, topical)	General clinical use, ischemic stroke, various conditions	Ensure adequate oxygen during inhalation; avoid contaminated H_2; consult healthcare provider for high/extended doses
No contraindications shown when taken as directed	Headaches (2/121, 1.7%); nasal cavity dryness (1/121, 0.8%); no significant difference *vs* control	H_2-O_2 inhalation	Knee osteoarthritis	Proper device use; avoid excessive water intake
No adverse effects/toxicity observed	None reported (qualitative improvements in energy, sleep, defecation noted)	Oral hydrogen-rich coral calcium	Autoimmune diseases (RA, SLE)	Monitor for potential effects of other components (*e.g.*, calcium) in combined supplements
No adverse effects reported	None reported	H_2-saline infusion	RA, ischemic stroke	Ensure sterile preparation and professional administration for injections
No substantially negative effect	None reported (as defined by MCID)	Hydrogen-rich water	exercise-induced muscle damage in athletes	Adherence to recommended dosages

GRAS: Generally recognized as safe; FDA: Food and Drug Administration; MCID: Minimum clinically important difference; RA: Rheumatoid arthritis; SLE: Systemic lupus erythematosus.

incorrect hydrogen-to-oxygen ratios, potentially leading to hypoxia. It is crucial for healthcare providers to ensure adequate ventilation and precise device calibration to mitigate these risks. Commercial HRW products and generating devices also exhibit significant variability in hydrogen concentrations. In the absence of standardized quality control measures, patients may receive subtherapeutic doses or experience inconsistent exposure. This underscores the need for regulatory oversight of hydrogen preparation techniques and protocols for verifying concentration levels. For future clinical applications, the establishment of rigorous quality control standards is essential. These should include requirements for hydrogen purity exceeding 99.9%, reliable concentration verification, and shelf-life stability. Additionally, protocols for device maintenance and comprehensive user training programs should be mandatory to ensure safe and effective clinical implementation.

LIMITATIONS

Despite encouraging preclinical and pilot data, several limitations constrain clinical translation of H_2 for musculoskeletal disorders. Most human trials remain small (n = 12-24) and brief (4 days to 1 month)[1,22,38]. In KOA, benefits waned by 12 weeks after a 2-week intervention[24]. Many studies lack placebo controls, use partial blinding (KOA: Open-label with blinded assessors[24]), or report high protocol variance[36]. Without progression to large, multi-center RCTs, findings risk remaining "promising but unproven". Delivery methods also vary widely HRW, inhalation, saline, topical, capsules with inconsistent dosing[22,36]. Outcomes span subjective scales (reduced perceived exertion, Visual Analog Scale, Western Ontario and McMaster Universities Arthritis Index, Brief Fatigue Inventory-Taiwan) and biomarkers (creatine kinase, IL-6, TNF-α, matrix metalloproteinase-3, 8-OHdG), with mixed effects on CRP and erythrocyte sedimentation rate [38]. Mechanistic data are sparse in humans; while preclinical models implicate Nrf2, JNK, NF-κB, and ROS scavenging [1], whereas the most clinical work lacks molecular endpoints[23]. Improvements in muscle atrophy were shown histologically, but precise pathways remain undefined[23]. Variable H_2 concentrations across devices, uncertain minimal doses, and adherence challenges hinder reproducibility. Animal models (*e.g.*, Achilles tendinopathy) also show poor validity and high bias[47]. Progress requires standardized dosing, validated delivery, biomarker-driven human trials, and rigorous preclinical models alongside well-powered RCTs.

FUTURE DIRECTIONS

Advancing molecular H_2 therapy in musculoskeletal care requires large, rigorously designed randomized controlled trials. Existing studies are predominantly small, short-term, and methodologically limited. Future trials should be multi-center, double-blind, placebo-controlled, with larger sample sizes and longer follow-up to evaluate sustained efficacy. Optimizing dosing protocols remains essential. Comparative studies on oral, inhalational, and topical delivery will help tailor strategies for specific musculoskeletal conditions. Translating preclinical findings to clinical practice demands integration of mechanistic biomarker analysis - targeting cytokines, oxidative stress indicators, and tissue-specific degradation markers - to validate pathways observed in animal models. Given H_2's safety profile, its role as an adjunct to standard treatments warrants deeper exploration. Research should assess whether it improves adherence, accelerates recovery, reduces adverse effects, and enhances patient-reported outcomes. Improved preclinical modeling is also critical.

Many current tendinopathy models utilizing hydrogen therapy lack translational accuracy. Standardized, high-fidelity models would better reflect human musculoskeletal pathology and support robust clinical application of H_2 therapy.

CLINICAL PRACTICE RECOMMENDATIONS

Based on current evidence, H_2 therapy may be considered as adjunctive treatment for osteoarthritis and rheumatoid arthritis in research settings only. Recommended protocols: HRW 1-2 L/day at 1-5 ppm for 4-12 weeks with standard care monitoring. Clinical implementation requires institutional review board approval and informed consent regarding experimental status.

CONCLUSION

Although H_2 demonstrates encouraging potential as an adjunctive treatment across a range of musculoskeletal disorders, its integration into routine clinical practice remains premature without robust, large-scale standardized trials. However, its excellent safety profile - especially when compared to conventional therapies - and preliminary evidence of efficacy in conditions such as osteoarthritis and rheumatoid arthritis underscore the need for continued, rigorous investigation rather than premature dismissal.

FOOTNOTES

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