

Clinical Application of Hydrogen Molecules in the Musculoskeletal Conditions

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Abstract

Hydrogen is an antioxidant targeted specifically at the harmful hydroxyl and peroxynitrite. Since the landmark study by Oshawa in 2007, the number of studies on hydrogen has increased significantly. While most studies are on animals, there are some clinical studies on humans. Hydrogen-rich water and hydrogen gas have been studied as a possible treatment for chronic conditions, including certain neurodegenerative diseases, ischemia and reperfusion injury, and even cancer. Studies involving musculoskeletal disorders, however, are few. In this paper, we attempt to review the role of molecular hydrogen in managing various acute or chronic musculoskeletal conditions. Ten studies on different human musculoskeletal disorders, including soft tissue injuries, ankle sprain, rheumatoid arthritis, psoriatic arthritis, Parkinson's disease, and myopathy, were identified. The review shows that hydrogen molecules may be an effective adjunctive treatment in managing early rheumatoid arthritis and psoriatic arthritis. However, many of the studies are case reports or prospective studies, and evidence for using hydrogen in managing musculoskeletal conditions is low. Further studies are required to establish if hydrogen administration has a place in managing orthopedic and rheumatic diseases.

Keywords: Hydrogen; Musculoskeletal; Sports Injury; Rheumatoid Arthritis; Psoriasis; Parkinson's Disease

Abbreviations

VAS: Visual Analog Scale; RCT: Randomized Controlled Trial; DMDS: Disease-Modifying Drug; DAS28: Disease Activity Scale of 28 Joints; CRP: C Reactive Protein; ACPAs: Antibodies against the Cyclic Citrullinated Peptides; PASI: Psoriasis Area and Severity Index; UPDRS: Unified Parkinson's Disease Rating Scale

Introduction

Hydrogen is the smallest molecule capable of penetrating through the cell membrane. Ohsawa and colleagues [1] showed that molecular hydrogen significantly reduced cerebral infarction in rats after occlusion of the left middle cerebral artery. They attributed the effects to the antioxidant properties of molecular hydrogen, which they postulated to be a specific antioxidant, selectively eliminating the harmful hydroxyl ($\cdot\text{OH}$), and to a lesser extent, the peroxynitrite (ONOO^-) radicals. Subsequent studies have shown that molecular hydrogen selectively eliminates the highly reactive hydroxyl radicals, but not the superoxide, peroxide, and nitric oxide, which are oxidants essential for cellular functions [2].

Recently studies investigating hydrogen molecules' clinical application and underlying mechanisms have increased significantly [2]. Many of the studies were in animals, investigating the effects of hydrogen molecules on the regulation of cytokines, oxidation stress, and their possible clinical applications [3]. Animal studies have been performed on many conditions; they include atopic dermatitis, cancer, diabetes mellitus type 2, metabolic syndrome, hemodialysis, inflammatory and mitochondrial myopathies, brain stem infarction, neurodegenerative diseases, and radiation-induced adverse effects [2].

Recently, clinical trials have been conducted on humans. The effects of hydrogen-enriched water and hydrogen gas have been evaluated in many conditions, including neurodegenerative diseases, ischemia and reperfusion injury, psoriasis, psoriasis-related arthritis, rheumatoid arthritis and different types of carcinoma. The outcome of many studies has been positive. However, studies involving musculoskeletal disorders are few [4]. We thus attempt to review the clinical role of hydrogen in managing various musculoskeletal conditions.

Materials and Methods

Papers were searched in PUBMED, using the Boolean search operators, (“Hydrogen” AND “Rheumatoid Arthritis,” “Hydrogen” AND “Sports Injury,” “Hydrogen” AND “Psoriasis,” “Hydrogen” AND “Gout,” “Hydrogen” AND “Parkinson’s disease,” “Hydrogen” AND “Pain,” and “Hydrogen” AND “Medical Treatment”), covering the year 2007 to December 2021. We excluded papers performed on animals, including biochemical changes and clinical studies. Non-English articles are also excluded. We include only studies conducted on humans and on musculoskeletal conditions. In addition, we include case reports, retrospective studies, prospective studies and controlled clinical trials.

Results

We have identified ten relevant papers covering the use of hydrogen molecules in musculoskeletal medicine. Two articles are on ankle sprain, one on soft tissue injuries, one on rheumatoid arthritis, one on psoriatic arthritis, four on Parkinson’s disease and one on myopathy. We thus reviewed the papers.

Soft tissue injuries

Topical and oral hydrogen-rich water has been evaluated for its effectiveness in managing soft tissue injuries [5]. The study recruited thirty-six professional athletes within 24 hours after injuries. They were examined by a certified sports medicine specialist and were randomly assigned to one of the three groups. Those in the control group received standard treatment protocol for soft tissue injuries. The first experimental group took hydrogen-rich water (oral hydrogen-rich tablets 2 gm/day) in addition to the standard protocol. Apart from receiving the conventional and oral hydrogen-rich water, the second experimental group was treated with topical hydrogen-rich packs (6 times per day for 20 minutes each). Evaluation of the condition was made at baseline, at the time of injury, and at 7 and 14 days post-injury.

Results showed those who received both oral and topical hydrogen intervention in addition to standard management recovered faster than the control group; the flexion and extension range of motion of the injured limb returned more quickly to the normal joint range [5]. The study did not report any statistical data.

Ankle sprain

Javovac, *et al.* reported a case of ankle sprain treated by supersaturated hydrogen-enriched water [6]. A 29-year-old male Caucasian professional football athlete sprained his right ankle and was subsequently diagnosed with a Grade II ankle sprain. Instead of the standard RICE protocol, which involves rest, ice, compression, and elevation, he was treated by six sessions of supersaturated hydrogen-rich water, each for 30 minutes, every 4 hours in the 24 hours immediately post-injury. The supersaturated hydrogen-rich water is prepared by putting magnesium-producing formulation (10g) into a 3-L stationary whirlpool with tap water of neutral temperature (20°C). The hydrogen gas present in the water is estimated to be around 8ppm. Subsequent assessment 24 hours post-injury showed that the visual analog scale (VAS) for pain reduced; it dropped from 50 points (moderate pain) at baseline (immediately after injury) to 20 points (mild pain). Also, ankle swelling decreased by 2.8%, and dorsiflexion range of movement improved by 27.9% from baseline to follow-up, respectively, with the ability to bear weight.

The same group subsequently performed a randomized controlled trial (RCT) to compare the effectiveness of supersaturated hydrogen-enriched hydrotherapy with the RICE protocol in treating acute ankle sprain [7]. Young adult professional athletes (age 23.7 ± 4.0 years) who sprained their ankles were randomly assigned to the intervention group (the hydrogen-enriched water group) and the RICE protocol group. The hydrogen group received the same treatment protocol as described; the patients had their injured limbs immersed in supersaturated hydrogen-enriched water for 30 minutes, at four-hour intervals, for six times within the 24 hours post-injury. For the RICE group, ice packs were applied for 20 minutes every 3 hours, with the injured ankle compressed with an elastic bandage for 24 hours and elevated at all possible times above the heart level. The outcome of the two methods is similar in terms of ankle swelling, range of motion, and single-leg balance with eyes open, suggesting that hydrotherapy with hydrogen-enriched water is not inferior to the standard RICE protocol in treating acute ankle sprain [7].

Rheumatoid arthritis

Hydrogen-enriched water has also been evaluated in the management of rheumatoid arthritis. Ishibashi, *et al.* (2012) assessed the effects of drinking hydrogen-rich water on 20 rheumatoid arthritis patients [8]. Five of them had early rheumatoid arthritis and were diagnosed less than 12 months before being admitted to the study; four did not receive any medication. The other 15 received disease-modifying drugs (DMDS) and/or biologics. For four weeks, all the patients were instructed to drink 530 ml of water containing 4 - 5 ppm of hydrogen daily. The patients then stopped drinking the hydrogen-rich water for four weeks, as a wash-out period, after which they drank the same quantity of hydrogen-rich water for another four weeks. One of the outcomes measured was the disease activity scale of 28 joints (DAS28), using the C reactive protein (CRP).

Results showed that at the end of the study, all the twenty participants' disease activity scores (DAS28-CRP) improved; 16 had significant improvement, and 4 had no change in symptoms [8]. The improvement was significant in all the five patients who had rheumatoid arthritis less than 12 months and whose antibodies against the cyclic citrullinated peptides (ACPAs) were below the standard values; four of them became symptom-free at the end of the study. For ACPAs positive subjects, lower values fared better than those with higher values. The four patients with APCA below 100 U/ml at baseline had their disease activity improved; the response of three subjects was good, and the other moderate. Thus, overall, 47.4% of patients (9/19) achieved remission, except for the one in remission at baseline [8].

Psoriatic arthritis

Ishibashi, *et al.* (2015) followed up the studies of hydrogen on rheumatoid arthritis, evaluated the effects of hydrogen therapy in psoriatic arthritis in three patients [9]. Three methods were used to administer the hydrogen molecule, including the drop infusion of saline containing 1 ppm of the hydrogen molecule, inhalation of 3% of hydrogen gas, and drinking water containing a high concentration (5 - 7 ppm) of hydrogen. The outcome measures include the DAS28-CRP, psoriasis area severity index (PASI) score, and cytokine levels. The parameters were determined at baseline and following each hydrogen treatment.

Results showed that the hydrogen intervention decreased all three patients' DAS28 and PASI scores regardless of the administration method [9]. Also, the psoriatic skin lesions almost disappeared at the end of the treatment. More importantly, hydrogen therapy alone reduced the severity of psoriatic arthritis, despite discontinuing the disease modifying anti-rheumatic drug adalimumab in one case. Cytokine levels were shown to decrease in two cases. The response to the different modes of hydrogen administration varied in different patients. Hydrogen-rich water was partially effective in one patient and effective in another patient, whereas hydrogen gas inhalation was effective in the two patients who opted for the treatment [9].

Parkinson's disease

Yoritaka, *et al.* (2013) conducted an RCT to assess the efficacy of hydrogen water in Japanese patients with levodopa-medicated Parkinson's disease [10]. The study included seventeen participants, drinking 1000 mL of hydrogen water or placebo water per day for 48

weeks. The results showed significant improvements in Unified Parkinson's disease rating scale (UPDRS) in the intervention group, as compared to the control group.

The group conducted another RCT in 2018 with a larger sample size and a more extended follow-up period [11]. This study involved 178 participants with a follow-up period of 72 weeks. The results, however, differed from that of previous study, showing no significant differences in change in total UPDRS score between the hydrogen water group and placebo water group.

In response to the contradictory results obtained in the previous two studies [10,11], Yoritaka, *et al.* (2021) conducted another RCT to ascertain if hydrogen gas inhalation benefits patients with Parkinson's disease [12]. Results showed that the inhalation of molecular hydrogen did not benefit patients with Parkinson's disease, though drinking hydrogen water or inhaling molecular hydrogen was safe and well-tolerated.

Yet, Hong, *et al.* (2021) reported that a combination of infra-red irradiation and hydrogen-rich water improved the severity of symptoms in patients with Parkinson's disease [13]. They recruited 18 patients aged between 50 and 78 years old, with Parkinson's disease, with Hoehn and Yahr stage II and III. They included patients with bilateral or midline involvement without balance impairment and patients with mild to moderate disability with impaired postural reflexes and are physically independent. The patients received concomitant infra-red light treatment and hydrogen-rich water, with the rationale being that hydrogen-water treatment would reduce the reactive oxygen species generated from the infra-red light application.

The light-emitting diode array with near-infrared (940 ± 10 nm) wavelength and intensity of $6.0 \text{ mW/cm}^2 \pm 10\%$ was placed inferior to the suboccipital area in the midline, directing towards the midbrain [13]. The treatment was conducted for 30 minutes for each patient for five consecutive days. Then, the treatment was suspended for two days and was continued for another week. The patients drank one can of hydrogen-rich water during the treatment intervention, 200 ml in volume and containing 2.5 ppm of dissolved hydrogen. UPDRS was used as the outcome measure. Results showed that the severity of UPDRS (sum of Part I, II, and III scores) decreased significantly after one week. The reduction continued for the second week, but after cessation for one week, the total score increased but still improved compared to the baseline [13].

Myopathies

The effects of molecular hydrogen in myopathies have also been studied [14], as molecular hydrogen has significant effects on more than 30 animal models of oxidative stress-mediated and inflammatory diseases.

The investigation involved an open-label trial and a randomized double-blind study. In the open-label study, patients with progressive muscular dystrophy, polymyositis/dermatomyositis, and mitochondrial myopathies were instructed to drink 1.0 litres of hydrogen-enriched water a day for 12 weeks. In the follow-up randomized, double-blind, placebo-controlled crossover trial, the patients were instructed to drink 0.5 litres of hydrogen-enriched water a day for eight weeks. The two trials showed that hydrogen-enriched water did not change patients' clinical symptoms. However, hydrogen improves mitochondrial dysfunction and inflammatory processes in patients with mitochondrial myopathies and polymyositis/dermatomyositis, respectively [14].

Discussion

There are few studies relating to the use of hydrogen molecules in the treatment of musculoskeletal conditions. Many of the studies are case reports or prospective studies, and there are few randomized, controlled studies. Thus, the evidence suggesting the use of hydrogen in the treatment of musculoskeletal conditions is very low.

Case reports suggested that hydrogen therapy may be of benefits in the treatment of soft tissue injuries, ankle sprain and inflammatory arthritides. The use of hydrogen molecule as an adjunctive treatment of early rheumatoid arthritis and psoriatic arthritis are particularly promising [8,9,15]. Both arthritides are chronic diseases that require long-term medication, and affect the well-being of the patients. Hydrogen-rich water and hydrogen gas inhalation, which are home treatments, may complement the medical treatment. Yet, the clinicians have to be aware that only case reports or prospective studies suggest their effectiveness in the two types of arthritides.

Hydrogen as a lone therapy has not been found to benefit Parkinson's disease [11,12]. Case reports, however, have shown that when it is coupled with infra-red therapy, it improves symptoms of Parkinson's patients, but only during the intervention [13]. Cessation of the intervention was accompanied by an increase in UPDRS score [13].

Hydrogen therapy, however, has not been found to benefit different forms of myopathies [14].

Conclusion

Our review showed that there are few studies on the effects of hydrogen therapy on musculoskeletal conditions. Of the different conditions, hydrogen shows promise as an adjunctive treatment of early rheumatoid arthritis and psoriatic arthritis. Yet, the evidence to support its effectiveness is low. Further studies are thus required to establish if hydrogen administration has a place in managing orthopedic and rheumatic diseases.

Conflict of Interest

The authors declare no conflict of interest.

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