OPINION ARTICLE

Should hydrogen therapy be included in a musculoskeletal medicine routine? [version 1; peer review: 2 approved]

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Abstract

Molecular hydrogen (H₂) has recently been recognized as a potential novel therapeutic agent in biomedicine. Initially proposed to be a possible treatment for certain types of neuromuscular disorders, cardio-metabolic diseases and cancer, H₂ improved clinical end-points and surrogate markers in several clinical trials, mainly acting as an anti-inflammatory agent and powerful antioxidant. In this paper, the medicinal properties of H₂ in musculoskeletal medicine are discussed with the aim to provide an updated and practical overview for health professionals working in this field.

Keywords

FDA, Molecular hydrogen, Rheumatoid arthritis, Soft tissue injury

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Background
As the oldest and the most abundant molecule in the universe, molecular hydrogen (H₂) has been traditionally recognized as a biologically inert gas. However, several trials in the past 10 years reported beneficial effects of H₂ in the clinical environment, revealing its possible role as a novel therapeutic agent in medicine. Usually administered orally or via inhalation, H₂ improves both patient- and clinician-reported outcomes, and biomarkers of different pathologies and disorders, from metabolic diseases to chronic systemic inflammatory disorders to cancer (for detailed review see Ref. 6). Its clinical relevance seems to be particularly notable in the musculoskeletal medicine, with several small-scale short-term studies reporting that H₂ was able to restore the health and functional abilities of patients after acute injuries or chronic illnesses affecting the muscles and bones. Since musculoskeletal conditions account for a large proportion of a general practitioner’s workload, one might consider H₂ as a promising medication or adjuvant that could alleviate these prevalent conditions. In this opinion paper, the medicinal properties of H₂ in musculoskeletal medicine are discussed to provide an updated and practical overview for health professionals working in this field.

Promising results from preliminary studies
Being prompted by the prominent effects of H₂ on disseuse muscle atrophy, cartilage trauma, and osteopenia in animal studies, a number of clinical investigators from 2010 onwards evaluated the effectiveness of H₂ in patients suffering from different muscle and bone ailments – from sprains and strains to chronic joint disorders to myopathies. Typically, these studies were designed as single-blind pilot trials, with small sample sizes (< 40 participants) and of short duration (≤ 12 weeks). Although limited in size and scope, those studies can provide early support for specific therapeutic claims about H₂ in musculoskeletal medicine. In a first trial, a combination of oral and topical H₂ resulted in a faster return to normal joint flexibility in 36 young men who had suffered sports-related soft tissue injuries, when administered for 14 days as a complementary treatment to a traditional medical protocol for soft tissue injuries. H₂ intervention (hydrogen-rich packs 6 times per day for 20 min and 2 g of oral H₂ daily) was found to augment plasma viscosity decrease after an injury, while other biomarkers of inflammation (C-reactive protein, interleukin-6) and clinical outcomes (pain scores at rest and at walking, degree of limb swelling) were not affected by the intervention. Another study in Japan reported that drinking 530 ml of a liquid containing 4 to 5 ppm of H₂ every day for 4 weeks significantly reduced disease activity in 20 patients with rheumatoid arthritis, as evaluated by changes in the degree of tenderness and swelling in 28 joints and C-reactive protein levels. H₂ was administered as an adjuvant to regular disease-modifying anti-rheumatic drugs and biological drugs, with the efficacy of H₂ found to be not inferior comparing to abatacept, methotrexate or a combination of two. In total, 47.4% of patients went into remission, with anti-citrullinated protein antibody (ACPA)-positive patients (ACPA levels above 300 U/mL; patients with worse prognosis and higher rates of erosive damage) responding best to the treatment. Finally, the consumption of water containing a high concentration of H₂ (31% saturation) for up to 12 weeks improved surrogate markers of muscle pain and fatigability in 22 patients with inherited and acquired myopathies treated with low-dose prednisone. Taken together, the above studies seem to pave the way for a future use of H₂ therapy in musculoskeletal medicine.

Take it with a grain of salt
Compared with conventional treatment protocols in musculoskeletal medicine, based on drugs and methods that are well-described with respect to efficacy and safety, H₂ still has a long journey ahead before it can be recognized as a common remedy in this medical discipline. At the moment, H₂ therapy is not adequately described in terms of approval, labeling, side effects, and pharmacovigilance information in musculoskeletal medicine. There are no dose escalation studies yet, and the optimal and safest dose range for H₂ remains unknown; furthermore, no federal agency or institutional entity provides appropriate patient counseling information about H₂. The US Food and Drug Administration (FDA) recently issued a notice (GRAS Notice No. 520) of a claim that the use of H₂ solubilized in water (up to a concentration of 2.14%) is generally recognized as safe (GRAS) when it is added to beverages and beverage containers in order to prevent oxidation. Based on the information provided by the H₂ gas-manufacturing company, as well as other information available to the FDA, the agency had no questions about the conclusion that hydrogen gas is GRAS under the intended conditions of use. However, the FDA has not made its own determination regarding the GRAS status of the subject use of H₂ gas. This seems to be the only formal information currently available concerning the use of H₂ in food or medicine! Despite this lack of formal approval, there are many formulations and devices widely available in the market that claim to supply H₂ for the use in musculoskeletal disorders, from gas-producing machines to dietary supplements and beverages, with H₂ amount varying greatly across the different products. Consequently, consumers might be exposed to easy-to-acquire but questionable products containing H₂.

Among other important medical issues that need to be addressed, including long-term safety or pharmacokinetics, the main question remains whether H₂ should be considered as a dietary supplement or a medicine, since the FDA declares that a product intended for inhalation (such as H₂ gas) is not a dietary supplement. Therefore, considering H₂, or at least some H₂ forms, for much stricter assessment and regulation by formally recognizing it as a drug in the future, might be more appropriate for this promising bioactive gas. So, it will take many more studies and tighter regulation before H₂ therapy can be endorsed as a routine protocol (or adjuvant to standard treatment) in musculoskeletal medicine. In the meantime, H₂ should be regarded as an experimental agent and not recommended to treat muscle or bone conditions in the general population.

Competing interests
No competing interests were disclosed.

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References

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The title is appropriate with reference to the content of the article.

The article is a review of the literature with reference to utilizing molecular hydrogen to enhance sports related injuries.

After a detailed review of the literature, the conclusion is there is not enough information to make any solid recommendation concerning utilizing molecular hydrogen to treat sports related injuries, so the implication is probably molecular hydrogen doesn't improve recovery from sports related injuries enough to make any difference.

This appears to be a good review of the related literature.

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

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This opinion paper provides an undated and practical overview on the properties of molecular hydrogen in musculoskeletal medicine. The paper focuses on the preliminary studies of H2 on musculoskeletal medicine, and the concerns over the general use of products containing H2. I sympathize the author’s prudent attitudes, which toward the hydrogen should be regarded as an experimental agent and not recommended to general use provisionally. However, I think this paper should also mention the long-term diving practices which high pressure hydrogen inhalation involved to prove the possible safe use of H2 gas.

**Competing Interests:** No competing interests were disclosed.

We confirm that we have read this submission and believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 08 Dec 2016  
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This comment is well taken. Several preliminary studies indeed reported a relative safety of H2 inhalation in humans. The mixture of hydrogen, helium and oxygen (Hydra 10) was safely used in the deepest recorded diving (701 m) in an on-shore hyperbaric chamber (Lafay et al. Undersea Hyperb Med 1995;22:51–60). Another study reported no physiological disturbances in patients with cerebral ischemia after exposed to inhalational H2 (Ono et al. Med Gas Res. 2012;2:21). Our group demonstrated no side effects of gaseous H2 in women with age-related cognitive decline (Ostojic et al. 2016, unpublished data). Nevertheless, more studies are needed to confirm the long-term safety of H2 gas in clinical environment, including musculoskeletal medicine.

**Competing Interests:** No competing interests to decline.