A systematic literature review of the effects of molecular hydrogen during exercise

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In the last decade, use of molecular hydrogen, through hydrogen-rich water (HRW), has become commonplace in the sports industry with anecdotal claims of improving athletic performance and endurance. Publications, clinical trials, and case studies have begun to emerge with the growing interest to clinically-validate the claims of improved performance and recovery in the athletic population. The objective of the current article is to review the recent literature to understand the effects of molecular hydrogen, through ingestion of hydrogen-rich water on muscles, joints, and athletic performance during the peri-exercise period. The following literature review documents the relevant effects identified within the included studies. A review of the studies published in the last ten years (2012-2022) pertaining to hydrogen-rich water (HRW) was performed. Using the PubMed search engine, the terms “hydrogen water” and “athlete” were searched. Quantitative data points pertaining to cardiorespiratory variables, blood markers, subject reported outcome measures, and athletic performance were identified from the included studies. Based on the aforementioned search criteria, one hundred and one articles were identified. Among these, fourteen studies pertained to the effects of molecular hydrogen during exercise. Of these studies, eleven studies reported the clinical findings associated with oral ingestion of liquid HRW and three studies identified observations pertaining to other hydrogen-rich applications in transdermal and tablet forms. The recent literature suggests that HRW may provide anti-inflammatory benefits as a neutralizing agent without evidence of side effects during high-intensity exercise in trained athletes. Consequently, when used during the peri-exercise period, HRW may be associated with anti-fatigue effects and improved athletic performance. The identified evidence supporting the use of HRW during the peri-exercise period is limited, and its extrapolation should be performed with caution. Despite the lack of significant high-quality evidence available in the recent literature, molecular hydrogen, through ingestion of HRW, has been adopted in the sports industry for its antioxidant, anti-inflammatory, and anti-fatigue properties identified in trained athletes, and it is used anecdotally to impact athletic performance without significant observed risk of side effects.

Keywords: hydrogen water, hydrogen-rich water, HRW, athlete, exercise

The medical application of molecular hydrogen in humans was originally documented approximately half a century ago and has since been evaluated in various clinical contexts [1, 2]. In the past decade, the sports industry has utilized molecular hydrogen and other buffering agents to increase the body’s antioxidant response and improve the efficiency of aerobic and anaerobic metabolism, anecdotally leading to improved athletic performance during high intensity exercise [2-4]. Enabled by its size, molecular hydrogen works through rapid diffusion into living tissues and cells [2]. The hydrogen (H2) molecule can penetrate through the cell membrane and the mitochondria where it helps to maintain a state between oxidation and reduction and maximize aerobic energy production [5]. Molecular hydrogen can be administered by different methods (inhalation of H2 gas or as injectable saline solutions, topical packs, or tablets), but one of the most common ways is the oral ingestion of hydrogen-rich water (HRW) [2, 4-6]. HRW has a pH higher than normal water and has become commercially available [7]. Recently, some studies have suggested it can improve athletic performance by reducing exercise-related metabolic acidosis and antioxidant and anti-inflammatory responses and delaying the onset of fatigue [7-9].
Methods
A literature review of the past ten years (2012-2022) with the search terms “hydrogen water” and “athlete” was conducted using the PubMed search engine. Prospective and retrospective studies that described the effects of molecular hydrogen on an athletic or exercising population were included. Non-clinical and animal studies, opinions, studies in a foreign language, studies with fewer than ten subjects (e.g. case reports), studies which did not pertain to the target treatment (molecular hydrogen) or the specified population (subjects exercising or athletes), and studies which could not be obtained were excluded. Study eligibility was initially determined by reading the title and abstracts. Studies meeting the eligibility criteria underwent a full-text evaluation. Any study which failed to meet the eligibility criteria after a full-text review was excluded. Quantitative data points pertaining to blood markers, subject reported outcome measures, cardiorespiratory responses, and athletic performance were identified from the included studies. The relevant findings of all included studies are identified in the current report along with an overview of the study.

Results
Based on the aforementioned search criteria, one hundred and one articles were identified. Among these, fourteen studies with three-hundred and twenty-one (321) subjects assessed the effects of molecular hydrogen during exercise and were included in the present report. Of these studies, eleven studies pertained to the oral intake of liquid HRW. Further, one study pertained to the transdermal application of liquid HRW, one study pertained to the oral intake of hydrogen-rich tablets (HRT), and one study described these latter two applications in two comparative cohorts.

The results of the following literature review support that HRW and other hydrogen-rich applications may have antioxidant, anti-inflammatory, and anti-fatigue properties and the potential to lead to improved performance and endurance in trained athletes during strenuous exercise. The antioxidant properties of molecular hydrogen can be supported by a reduction in the oxidative response indices, including superoxide anion (O2-) and MDA (malondialdehyde), and an increase in the antioxidant defense indices, SOD (superoxide dismutase) and T-AOS (total antioxidant capacity) [8, 10]. The anti-inflammatory effects of HRW can be documented through a reduction in inflammatory markers, including IL-1 (interleukin-1), IL-6 (interleukin-6), and TNF-α (tumor necrosis factor-alpha) [8]. The anti-fatigue effect of hydrogen-rich applications may be supported through reduction of blood markers (e.g. lactate), as well as, subject reported outcome measures identifying a reduction in fatigue (e.g. FI—fatigue index, fatigue assessment through VAS scores, RPE—ratings of perceived exertion) [2-4, 9]. As a result of the cumulative properties of molecular hydrogen, an improvement in performance has been identified in some studies through an increase in power and torque (e.g. MP—mean power, PP—peak power, and PT—peak torque) and a reduction in race times [2, 4, 5].

Hydrogen-Rich Water Liquid Form
In a randomized, double-blind, placebo-controlled study in Japan involving ten soccer players, the athletes received either placebo water or hydrogen-rich water (HRW) (free hydrogen content of 0.92-1.02 mM) and were examined twice in a crossover manner. In a period of eight hours, the subjects consumed 1,500 mL of placebo water or hydrogen water [4]. The athletes were subjected to two tests: 30 minutes of cycling exercise on an ergometer at 50 rpm/min at a 75% maximal oxygen uptake and 100 repetitions of maximal isokinetic knee extensions. The athletes underwent serum blood tests informing levels of lactate, oxidative stress markers (d-ROM—derivatives of reactive oxygen metabolites and BAP—biological antioxidant potential), creatine kinase, and measurement of peak torque (PT) through a biomechanical isokinetic device. While the no significant difference was found between the two groups in regards to the oxidative stress markers (d-ROM and BAP) and creatine kinase, sequential changes of blood lactate during exercise revealed that blood lactate levels were significantly reduced in the HRW group during the cycling exercise (p<0.05). The maximal difference was noted 45 minutes to 60 minutes post-exercise. Further, the authors found that peak torque was significantly higher in athletes who received the hydrogen water for the first forty repetitions of the 100 isokinetic knee extensions compared to those who received the plain water. The authors demonstrated that hydration with HRW reduced blood lactate levels and prevented a decrease of peak torque, which are indicators of muscle fatigue [4].
A randomized, double-blind, placebo-controlled crossover study in the Czech Republic with twelve sports science male students evaluated cardiorespiratory variables (minute ventilation—VE) and the ventilatory equivalent for oxygen—VE/VO2), lactate blood levels, and ratings of perceived exertion (RPE) after receiving 600mL of HRW (free hydrogen content of 0.5 ppm) or placebo water within 30 minutes prior to exercise performed on the bicycle ergometer [3]. The exercise protocol consisted of a 10-minute warm-up at a work rate of 1 W/kg (watts of cycling power produced per kilogram of body weight) followed by work rates of 2 W/kg, 3 W/kg, and 4 W/kg each lasting eight minutes with the participant cadence ranging between 70 and 80 rpm (revolution per minute). The aforementioned variables were assessed in the last minute of each work rate. At the highest intensity (4W/kg), participants who had HRW had significantly reduced blood lactate concentration (~16%), minute ventilation (VE) (~10%), ventilatory equivalent for oxygen (VE/VO2), and ratings of perceived exertion compared to their placebo baselines (p<0.05). However, at a lower intensity (3W/kg), participants who had the HRW only had significantly reduced lactate concentration with no significant difference in the remaining variables. No statistical differences were noted at work rates of 2W/kg. No significant differences were identified in the other studied variables namely heart rate, oxygen uptake (VO2), and respiratory quotient (RQ). The authors suggest that the HRW may have a stimulating effect on mitochondrial respiration and function resulting in enhanced aerobic ATP production and/or lactate oxidation resulting in the significantly lowered lactate levels. The authors further proposed that with HRW supplementation may be related to the lower level of muscle acidosis, which may have consequently induced lower CO2 production lowering the ventilatory response and improving ventilatory efficiency at maximum exercise intensities [3].

In a randomized, double-blind, placebo-controlled crossover study of sixteen male athletes in the Czech Republic, researchers studied the effects of HRW (with a free hydrogen content of 0.9 ppm) and placebo water when performing two 4.2 km up-hill races [11]. With 1,680 mL of the respective water administered 24 hours, 3 hours, 2 hours, and 40 minutes prior to each race, the races were performed one week apart. In the overall cohort, no significant difference was identified in race time (RT) and maximum heart rate (HR max) between the HRW group and the placebo group. However, analysis of the subgroup of the four slowest runners showed that the HRW treatment likely improved the race time and this finding was close to bearing statistical significance (p=0.07). The authors suggested that the magnitude of the anti-fatigue effect of HRW on muscle fatigue and consequently performance depends on the individual runner’s ability [11].

A randomized, double-blind, placebo-controlled crossover study in the Czech Republic reported on sixteen professional male soccer players who received HRW (free hydrogen content of 0.9 ppm) and placebo water prior to implementing a sprinting protocol [5]. The authors stated that the study illustrated the ergogenic effect of ingesting HRW prior to exercise on reducing sprint time. The volume of 1,260 mL of the respective water was administered in four doses prior to an experimental sprinting protocol. The athletes performed fifteen 15-meter and fifteen 30-meter sprints interspersed by 20 seconds of active recovery. The study identified that the athletes who received the HRW were able to significantly reduce the times of their final 15-meter sprints, 14th and 15th sprints, by 3.4% and 2.7%, respectively compared with when they had the placebo water (p<0.001). Similarly, when the athletes received the HRW prior to the 30-meter sprints, they were able to significantly reduce their sprint times by 1.9% compared to when they received the placebo water (p<0.001). No significant differences were identified in the other studies variables, namely heart rate and RPE. Regarding the significant findings, the authors suggested that hydrogen ingested as hydrogen-rich water may play a role in maintaining mitochondrial efficiency and peak muscle power output which manifested in the later stages of the repeated sprints protocol [5].

A randomized, single-blind, placebo-controlled crossover study was performed on eight trained male cyclists in Italy [7]. The participants were provided with two liters of placebo water or HRW (pH 9.8, free hydrogen content of 0.450 ppm) daily for two weeks prior to the exercise protocol. The protocol consisted of ten 16-second sprints in which the participants were encouraged to spring as fast as possible with an isokinetic modality at 100 rpm. The authors noted that the peak power output (PPO) reached a maximum after the second sprint. The PPO decreased significantly in the 8th and 9th sprints when
the athlete received the placebo water (p<0.05), and no significant decreases in PPO were identified when the same athletes ingested the HRW. No other statistically significant differences were noted among the other cardio-respiratory variables (i.e. VO2 max, HR max, and RER) over the course of the ten sprints. The authors concluded that two weeks of HRW intake may help in the maintenance of PPO in repetitive high intensity exercise [7].

In a randomized, double-blind, placebo-controlled study of 99 healthy participants with no habit of extensive of exercise in Japan, participants ingested 500 mL of HRW with a free hydrogen content of 0.8 ppm (N=52) or 500 mL of placebo water (N= 47) [9]. After 30 minutes, all participants exercised on a stationary bike for ten minutes with step-wise loading until the heart rate reached 75% of predicted maximum heart rate. Heart rate (HR) and oxygen uptake (VO2) were recorded during the exercise. The participants rated psychometric fatigue on the Visual Analog Scale (VAS) and provided a rating of perceived exertion (RPE) on the Borg’s scale. Prior to the experiment, baseline values for the listed variables were collected for all participants after drinking 500 mL of the respective water and performing the same exercise. Compared to baseline values, a significant decrease in heart rate of participants who were supplemented with the HRW was found compared to those who were given placebo water (p<0.05). Further, a significant reduction in fatigue was noted in the VAS psychometric fatigue assessment of participants receiving the HRW (p<0.05). No significant differences were noted pertaining to VO2 max and RPE on the Borg Scale [9].

A second randomized, double-blind, placebo-controlled experiment was conducted by the same researchers in Japan on sixty participants who regularly exercised and who did not consume HRW for at least 3 months [9]. The participants were given either 500 mL of HRW with a free hydrogen content of 1.0 ppm (N=30) or 500 mL of placebo water (N=30). After ten minutes, all participants performed moderate exercise on a stationary bike for eleven minutes with step-wise loading until the heart rate reached 75% of predicted maximum heart rate. Baseline and postexercise values for heart rate (HR), maximal oxygen uptake (VO2 max), psychometric fatigue (VAS score), and ratings of perceived exertion (RPE) were collected for all participants after drinking 500 mL of the respective water. A significant increase in VO2 max was noted in the participants who were given HRW (p<0.05), while little to no change was identified in the participants who received the placebo water during the experiment. Further, a significant reduction in tiredness was noted through the Borg Scale for RPE in participants receiving the HRW (p<0.05). No significant differences were noted in HR max and subject reported fatigue on the VAS. The authors reported that while the statistically significant findings were different for each population (untrained subjects compared with trained subjects), the study supports that HRW provides enhanced endurance capacity as assessed by VO2 max in moderate exercise of trained subjects and alleviated psychometric fatigue after mild exercise in untrained subjects. The authors noted that the average VO2 max was significantly higher for the participants of the second study compared to the first. Therefore, it was suggested that the additive effects of HRW on an elevated VO2 max capacity in participants who exercised regularly may result in enhanced endurance [9].

In a randomized, double-blind, placebo-controlled crossover study of fourteen endurance-trained male runners in Malaysia, researchers studied the effects of 290 mL of HRW or placebo water during and after exercise [12]. The participants underwent six four-minute submaximal running bouts, as well as, a maximal incremental running test, which involved running until exhaustion. The water was provided within 10 minutes of the exercise tests. Maximal heart rate (HR), respiratory exchange ratio (RER), ratings of perceived exertion (RPE), minute ventilation (VE), maximum oxygen uptake (VO2), and carbon dioxide production (VCO2) were collected. No statistical significance was found with this volume of HRW. The authors concluded that with the ingestion of 290 mL of HRW prior to submaximal treadmill running and a subsequent dose prior to running to exhaustion was not sufficient to induce an ergogenic effect in the athletes. The authors suggested that the size of the dose was not sufficient to modulate the buffering capacity during intense endurance in trained athletes [12].

In a study of nineteen healthy males in Serbia, researchers studied the effects of daily oral administration of HRW (free hydrogen concentration of 1.1 mM/L) for seven days on baseline arterial pH and the rate of acidosis induced by exercise [13]. From the start to the end of the intervention period (day 7), participants underwent blood sampling and endurance running daily. The researchers found that
HRW significantly increased fasting arterial blood pH by 0.04 and postexercise pH by 0.05 (p<0.05). The researchers found no adverse effects. The authors reported that the findings of the study support that HRW may provide benefits as a neutralizing agent [13].

In a comparatively longer-term study, researchers evaluated the effects of two months of HRW consumption in juvenile female soccer players in China in a randomized, single-blind, placebo-controlled trial [8]. The thirty-eight athletes were split into a control group (N=10) and a hydrogen-rich water treatment group (N=28). Approximately 1.5 to 2 liters of water were consumed daily for eight weeks. After eight weeks of exercise, the authors reported a significant increase in hemoglobin (Hgb) levels in the group receiving the HRW group (from 129.59g/L to 139.89g/L) compared to the increase identified in the control group (from 124.00g/L to 131.60g/L) (p<0.05). Blood tests further identified significantly lower levels of malondialdehyde (MDA) (an oxidative stress marker) and higher levels of the antioxidant defense indexes, superoxide dismutase (SOD) and total antioxidant capacity (T-AOC), for the HRW group compared to the control group (p<0.05). Inflammatory markers (IL-1, IL-6, and TNF-α) were also measured at the culmination of the 8-week period and found to be significantly lower in the HRW group than for the control group (p<0.05). No significant differences were noted in the remaining blood test variables (blood urea nitrogen—BUN and creatine kinase—CK). The findings suggested that the effects of HRW may enhance the hemoglobin level, have antioxidative properties, and exert an anti-inflammatory effect on the athletes [8].

In a randomized, double-blind, placebo-controlled study of sixty swimmers in China, thirty (N=30) were treated with 200 mL of HRW three times daily for a period of eight days (HRW group), and thirty received the same quantity of placebo mineral water (control group) [10]. The free radical marker: superoxide anion (O2-), and antioxidant defense markers: SOD (superoxide dismutase) and T-AOC (Total Antioxidant Capacity), were monitored through blood work prior to swimming exercise and two hours post-exercise. Results showed a significant reduction in serum superoxide anion (O2-) in the HRW group (p<0.05). While there was no statistical difference in the serum superoxide anion activities of the two groups prior to exercise (HRW group: 143.18 U/ml; control group: 146.60 U/ml), the athletes who received the HRW had a significantly lower level of serum superoxide anion after exercise (98.96 U/ml) compared to those who received the placebo water (117.17 U/ml) (p<0.05). Further, the study reported that athletes receiving HRW had a significantly higher level (p<0.05) of antioxidant markers (SOD: 66.92 U/ml and T-AOC: 3.36 U/ml) compared to athletes receiving the placebo mineral water (SOD: 45.65 U/ml and T-AOC: 2.36 U/ml) though the groups had no difference prior to the treatment. The results suggested that the HRW could inhibit the superoxide anion activity and reduce oxidative stress injury by preventing the free radical damage caused by high-intensity exercise [10].

A randomized, double-blind, placebo-controlled crossover study was performed to evaluate the ergogenic effect of seven days of HRW intake among 37 trained and untrained cyclists in Spain [2]. The participants drank between 1,920 and 2,240 mL of HRW (free hydrogen content of 1.9 ppm) or placebo water per day for seven days. The participants started at a work rate of 100W on a stationary bike with a cadence of 60-70 rpm. This rate was increased by 30W every two minutes until exhaustion. Lactate concentration was measured one minute after the end of the tests. The authors identified significantly lower blood lactate levels among trained and untrained cyclists with the supplementation of HRW (p<0.05). The other variables, namely cardio-respiratory variables (maximal oxygen uptake—VO2 max, percentage of VO2 max in the ventilatory anaerobic threshold—VT2%VO2 max, maximal work rate—W = max, maximum heart rate—HR max), RPE, and time to exhaustion (TTE), were not significantly affected by the supplementation of HRW. In addition, anaerobic tests were performed after the participants performed a warm-up at 100 W with a cadence of 60–70 rpm. During the first 20 seconds of the first test, the participants had to maintain a cadence greater than 130 rpm. After these initial seconds, if the participant was not able to maintain a pedaling cadence above 100 rpm, the resistance of the potentiometer was gradually lowered to maintain the highest power possible throughout the test. Following the test, subsequent anaerobic tests were performed to determine peak power (PP), mean power (MP), and fatigue index (FI). Compared to values identified with the placebo water, PP and MP were significantly higher and FI was significantly lower (p<0.05) when the participant drank the HRW the week prior to the
anaerobic test. This finding was only applicable to the trained cyclists and not the untrained cyclists. The authors suggested that the performance improvement in trained cyclists after the intake of HRW occurred due to a synergistic effect between the higher antioxidant and metabolic capacity of the trained cyclist with the added effect of the hydrogen-rich water, which allowed them to develop a greater and more lasting effort in anaerobic conditions, reaching higher power levels and lower fatigue [2].

<table>
<thead>
<tr>
<th>Reference</th>
<th>Design</th>
<th>No of subjects receiving HRW</th>
<th>Trained/untrained subjects</th>
<th>Exercise</th>
<th>Administration PPM mL Start time before exercise</th>
<th>Statistically significant findings compared to placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hydrogen-Rich Application: Liquid Form Oral Intake</strong></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Aoki et al., 2012 Test 1</td>
<td>RT, DB, PC, CO</td>
<td>10</td>
<td>Trained</td>
<td>30 minute bicycle ergometer</td>
<td>0.92-1.02 ppm; 1,500 mL 8 hours</td>
<td>↓Lactate</td>
</tr>
<tr>
<td>Aoki et al., 2012 Test 2</td>
<td>RT, DB, PC, CO</td>
<td>10</td>
<td>Trained</td>
<td>100 Isokinetic knee extensions</td>
<td>0.92-1.02 ppm; 1,500 mL; 8 hours</td>
<td>↑PT</td>
</tr>
<tr>
<td>Botek et al., 2019</td>
<td>RT, DB, PC, CO</td>
<td>12</td>
<td>NR</td>
<td>8 minute bicycle ergometer with stepwise increase in loading</td>
<td>0.5 ppm; 600 mL; 30 minutes</td>
<td>↓ Lactate ↓ VE ↓ VE/ VO2 ↓ RPE At highest loading</td>
</tr>
<tr>
<td>Botek et al., 2020</td>
<td>RT, DB, PC, CO</td>
<td>16</td>
<td>Trained</td>
<td>Two 4.2 km up-hill races</td>
<td>0.9 ppm; 1,680 mL; 24 hours</td>
<td>None</td>
</tr>
<tr>
<td>Botek et al., 2022</td>
<td>RT, DB, PC, CO</td>
<td>16</td>
<td>Trained</td>
<td>Fifteen 15-meter and fifteen 30-meter sprints</td>
<td>0.9 ppm; 1,260 mL; 2 hours</td>
<td>↓ Race time</td>
</tr>
<tr>
<td>Da Ponte et al., 2018</td>
<td>RT, SB, PC, CO</td>
<td>8</td>
<td>Trained</td>
<td>Ten 16-second sprints</td>
<td>0.45 ppm; 2000 mL; 2 weeks</td>
<td>↑ PP</td>
</tr>
<tr>
<td>Mikami et al., 2019 Test 1</td>
<td>RT, DB, PC</td>
<td>52</td>
<td>Untrained</td>
<td>10 minute bicycle ergometer with stepwise increase in loading</td>
<td>0.8 ppm; 500 mL; 30 minutes</td>
<td>↓ HR max ↓ fatigue</td>
</tr>
<tr>
<td>Mikami et al., 2019 Test 2</td>
<td>RT, DB, PC</td>
<td>30</td>
<td>Trained</td>
<td>11 minute bicycle ergometer with stepwise increase in loading</td>
<td>1.0 ppm; 500 mL; 10 minutes</td>
<td>↑VO2 max ↓ RPE</td>
</tr>
<tr>
<td>Ooi et al., 2020</td>
<td>RT, DB, PC, CO</td>
<td>14</td>
<td>Trained</td>
<td>Six 4-minute submaximal running exercises on a treadmill;Maximal incremental running test until exhaustion on a treadmill</td>
<td>NR ppm; 290 mL 10 minutes</td>
<td>None</td>
</tr>
<tr>
<td>Ostojic, 2012</td>
<td>SA</td>
<td>19</td>
<td>NR</td>
<td>Endurance running daily for one week NFDP</td>
<td>1.1 ppm 2,000 mL 7 days</td>
<td>↓pH</td>
</tr>
</tbody>
</table>

Table 1 Summary of clinical literature reporting the effects of hydrogen-rich water during exercise (continues next page).
Indicators were among which and myoglobin, white blood (WBC) protein markers infusion) minutes following 30 placebo supersaturated water into the volunteers exposed crossover Serbia, study healthy a randomized, which jeopardize In delayed to the reduce and stress Not water Forms Hydrogen-Rich pH—potential hydrogen; O2—superoxide anion. IL-1—interleukin-1; IL-6—interleukin-6; TNF-α—tumor necrosis factor alpha; NFDP—no further details provided; ppm=mM/L; further provided; necrosis PT—peak GPT—peak GPT—peak GPT—peak MDA—malondialdehyde; T-AOC—total antioxidant capacity, Hgb—hemoglobin; PP—peak MP—mean ventilation; index; power; equivalent for power; reported; rate; of oxygen HR VO2 PC—placebo-controlled; CO—crossover; DB—double-blind; PC—placebo-controlled; SA—single arm; PPM—(hydrogen) parts per million pertaining to HRW; NR—not reported; RPE—ratings of perceived exertion; HR max—maximum heart rate; VO2 max—maximum rate of oxygen consumption; PP—peak power; MP—mean power; FI—fatigue index; VE—minute ventilation; VE/VO2—ventilatory equivalent for oxygen; PT—peak torque; Hgb—hemoglobin; SOD—superoxide dismutase; T-AOC—total antioxidant capacity, MDA—malondialdehyde; IL-1— interleukin-1; IL-6—interleukin-6; TNF-α—tumor necrosis factor alpha; NFDP—no further details provided; ppm=mM/L; pH—potential hydrogen; O2—superoxide anion.

**Table 1** (continued from previous page). HRW—hydrogen-rich water; RT—randomized trial; DB—double-blind; SB—single-blind; PC—placebo-controlled; CO—crossover; SA—single arm; PPM—(hydrogen) parts per million pertaining to HRW; NR—not reported; RPE—ratings of perceived exertion; HR max—maximum heart rate; VO2 max—maximum rate of oxygen consumption; PP—peak power; MP—mean power; FI—fatigue index; VE—minute ventilation; VE/VO2—ventilatory equivalent for oxygen; PT—peak torque; Hgb—hemoglobin; SOD—superoxide dismutase; T-AOC—total antioxidant capacity, MDA—malondialdehyde; IL-1— interleukin-1; IL-6—interleukin-6; TNF-α—tumor necrosis factor alpha; NFDP—no further details provided; ppm=mM/L; pH—potential hydrogen; O2—superoxide anion.

**Hydrogen-Rich Application Water Transdermal Forms**

Not only has hydrogen-rich water been shown to reduce oxidative stress injury and muscle fatigue in athletes through consumption, but studies show even the topical application of HRW has also been shown to reduce muscular pathological processes associated with oxidative stress [6]. High intensity exercise may result in delayed onset of muscle soreness (DOMS) which may jeopardize the athlete’s exercise routine. In a randomized, double-blind, placebo-controlled crossover study in Serbia, six active, healthy male volunteers were exposed to DOMS-inducing eccentric leg press contractions and were immediately immersed up to the neck into a 200 L bathtub of supersaturated hydrogen-rich water (8mg of H2 per L) or placebo water (tap water with no hydrogen infusion) for 30 minutes [6]. The following blood markers were collected pre-exercise (baseline) and 24 hours after the exercise: creatine kinase (CK), lactate dehydrogenase (LDH), aspartate transaminase (AST), troponin, C-reactive protein (CRP), aldolase, myoglobin, and white blood cell (WBC) count. Among these, CK, AST, and aldolase, which are indicators of muscle damage, were significantly lower 24-hours after exercise for the subjects who had a hydrogen-rich water bath compared to those who had a placebo water bath (p<0.05). No other statistical significance was found among the remaining variables. Subject reported outcomes were collected through the Visual Analogue Scale (VAS) scores pertaining to muscle soreness. A significant difference between the groups after bathing and at the 24-hour follow-up was identified, and the greatest difference in soreness was found immediately after bathing (p<0.05). The hydrogen-rich water group experienced a 32.7% and 31.6% reduction in muscle soreness and the placebo group reported a 20.0% and 22.4% reduction after bathing and at the 24-hour follow-up, respectively. The results of this study support that transdermal supplementation of hydrogen-rich water reduces muscular damage and muscle soreness for up to 24-hours post high-intensity exercise compared to placebo water [6].

**Hydrogen-Rich Application Tablet and Transdermal Forms**

A randomized controlled, single-blinded study in Serbia with thirty-six professional athletes who suffered an acute lower extremity soft tissue injury were randomly assigned to one of three groups (N=12): a control group who received the traditional
treatment (rest, ice, compression, elevation—RICE protocol), a group who received the traditional treatment and was supplemented with 2 g of hydrogen through oral intake of four hydrogen-rich tablets three times per day for two weeks (HYD1), and a group who received the traditional treatment and was supplemented with 2 g of hydrogen via tablets in addition to a hydrogen-rich topical pack applied six times daily for 20 minutes (HYD2) [14]. At 14 days after the injury, the authors reported a moderate to large effect on pain scores when walking in the group supplemented with oral and topical hydrogen (HYD2) when compared to the control. While no significant differences were found in levels of CRP (C-reactive protein) or IL-6 (interleukin-6), the authors noted a significant increase in blood plasma viscosity (p<0.05). Further, the authors reported a significantly faster joint range of motion recovery for both flexion and extension in athletes who received the hydrogen-rich tablets and topical hydrogen-rich packs (HYD2) compared to the athletes who had the traditional treatment alone (p<0.05) [14].

**Hydrogen-Rich Application Tablet Forms**

In a randomized double-blind, placebo-controlled crossover study involving nineteen healthy subjects in the United States, the authors studied the effect of acute supplementation with hydrogen on respiratory rate (RR), heart rate (HR), and respiratory exchange ratio (RER) and oxygen volume (VO2) taken every 30 seconds during treadmill exercise [15]. To collect baseline values, the subjects walked on the treadmill at an initial speed of 2.7 km/h followed by an increase in speed and grade every 3 minutes until volitional exhaustion. The participants repeated the procedure after receiving either the placebo and the hydrogen-rich tablets, which the authors referred to as hydrogen-rich water tablets. The hydrogen-rich tablets (5mg of H2) or placebo medication were ingested the night prior to and 30 minutes before the exercise test. Among the aforementioned variables, the authors identified a significantly lower change in the average heart rate from the beginning (baseline) to the end of the exercise when the subjects had hydrogen-water supplementation (3.6 bpm higher) compared to the placebo (5.1 bpm higher). No other significant differences between the groups were identified. The results supported that the hydrogen-rich supplementation decreased the exercising heart rate without influencing oxygen consumption. Therefore, the authors speculated that the hydrogen-rich supplementation can improve oxygen extraction and utilization at the cellular level of the muscle [15].


Table 2 Summary of clinical literature reporting the effects of hydrogen-rich applications during exercise. HRW—hydrogen-rich water; RT—randomized trial; DB—double-blind; PC—placebo-controlled; CO—crossover; NR—not reported; NFDP—no further details provided; CK—creatine kinase; ALD—aldolase; AST—aspartate transaminase; soreness—as reported through the Visual Analog Scale; ROM—range of motion; HR max—maximum heart rate.

### Discussion

The use of HRW in sports medicine is a newer concept. Short-term clinical studies have begun to support the marketing of HRW as a nutritional aid, especially for those who experience strenuous exercise [13]. With a half-life of 0 to 2 hours, molecular hydrogen within HRW can rapidly penetrate the glass and plastic walls of any container and almost disappears after 8 hours; therefore, studies support rapid ingestion [13, 16].

The anti-acidity property of molecular hydrogen is well-documented through clinical studies assessing HRW [13, 17]. HRW exhibits a higher pH than that of plain water and may be beneficial in the treatment of exercise-induced acidosis, a common metabolic disturbance among active individuals [17]. This acidosis is characterized by a lower body pH and is accompanied by the build-up of lactate [17]. During vigorous exercise, cells are forced to rely on non-mitochondrial, anaerobic adenosine triphosphate (ATP) production which leads to proton (H+) release reducing the serum pH. As an acidity-lowering agent, HRW can mitigate the acidity produced during exercise and exert potential antioxidant, anti-inflammatory, ventilatory, and anti-fatigue effects which may culminate in enhanced physical performance in trained athletes during high intensity exercise [17]. These findings have been identified in the present study.
Antioxidant

In the current literature review, the oxidative stress markers, superoxide anion (O2-) and MDA (malondialdehyde), were noted to have significantly decreased, and the antioxidant defense indices, SOD (superoxide dismutase) and T-AOS (total antioxidant capacity), were noted to have significantly increased after the HRW treatment compared to placebo treatment during high intensity exercise in trained athletes [8, 10]. A prior study identified a statistically significant increase in antioxidant defenses by assessing the level of serum biological antioxidant potential (BAP) after four-weeks of HRW consumption compared to placebo water in healthy adults who were over 30 years of age [18]. It is postulated that the underlying mechanism is that the inert molecular hydrogen reduces free radicals (e.g. superoxide anion—O2- and hydroxyl radical—OH) when molecular hydrogen is administered through HRW [16, 18]. This reaction has been shown to selectively remove the superoxide anions and hydroxyl radicals without consistently and significantly affecting other reactive oxygen species (ROS), which may explain the lack of a significant reduction of some oxidative stress markers (d-ROM), as well as, the varied results regarding other antioxidative markers (BAP) for subjects treated with HRW as noted in the current report [8, 10, 18].

Anti-inflammatory

Molecular hydrogen has been shown to decrease the expression of various proinflammatory factors including interleukin (IL)-6, IL-1β, IL-10, IL-12, and tumor necrosis factor-α (TNF-α) [16, 19]. This finding was supported in the clinical literature pertaining to HRW but not to the other forms of hydrogen-rich supplementation (transdermal or oral tablets) provided in the current report [8]. While the reasoning for this discrepancy is unclear, it is theorized that HRW downregulates the secretion of proinflammatory cytokines thereby suppressing inflammation [16]. The production of excess inflammatory cytokines is a key response from the accumulation of lactate, which is produced and secreted in significant quantities by immune cells during glycolysis and causes a reduction of pH in the inflamed tissue [20]. During strenuous exercise, working muscles generate energy anaerobically and release lactate which modulates the release of proinflammatory cytokines [20, 21]. It theorized that the accumulation of molecular hydrogen prevents the dissociation of lactic acid into hydrogen (H+) and lactate and enhances mitochondrial lactate oxidation—thus preventing the eventual accumulation of inflammatory markers [3, 14].

Ventilatory

Lactate is a biochemical marker of the anaerobic contributions of ATP production [3]. While it is unclear whether HRW reduces anaerobic ATP production and/or improves aerobic mitochondrial efficiency, the findings in the current report support that hydrogen-rich applications significantly lower blood lactate [2-4]. It has also been proposed that these lower levels of lactate may be the result of potential HRW-induced ventilatory efficiency during high-intensity exercise. It is well-established that exercise-induced acidosis causes a temporary homeostatic impairment that compels immediate buffering through hypercapnic stimulating ventilation [3]. As noted in the current report, ventilatory efficiency was illustrated in some studies through a significant reduction in minute ventilation (VE) and ventilatory equivalent for oxygen (VE/VO₂), as well as, a significant increase in maximal oxygen consumption (VO₂ max) [3, 9]. However, this finding was not consistent across all included studies [2, 7, 12].

Anti-fatigue and Performance

Many of the studies pertaining to trained athletes included in the present research supports that peri-exercise ingestion of HRW has been shown to have an anti-fatigue effect (through fatigue tests and ratings of perceived exertion—RPE) and an enhanced performance effect across different modes of exercise through various performance outputs, including anaerobic power output during cycling, maximal muscle strength during isokinetic exercise, and race times during intermittent sprints [2, 4, 5, 9]. However, some studies, particularly those which included untrained participants exercising, identified no effect of HRW supplementation on RPE, indicative of tiredness [2, 9, 12]. Researchers suggested a synergistic effect between HRW consumption and trained athletes, who have a higher baseline antioxidant and metabolic capacity which allows them to resist fatigue and tiredness [2].

The increase in free radicals (e.g. superoxide anion—O2- and hydroxyl radical—OH) and other reactive oxygen species (ROS), which typically occurs during intense exercise, has been shown to cause...
mitochondrial damage, which is associated with increased fatigue and diminished performance [2]. Fatigue is caused through various mechanisms, including the accumulation of metabolites (e.g. lactate and H+) within muscle fibers which have often been suggested as being responsible for the decrease in muscle contractility [4]. In the current study, the improved muscle contractility with the supplementation of HRW was evidenced through an increase in power-related variables (peak power—PP, mean power—MP, and peak torque—PT), as well as, a reduction in race times in trained participants [2, 4, 5, 9]. These studies support that HRW has the potential to improve athletic performance by chemically reducing exercise-induced acidosis and delaying the onset of fatigue times [2, 4, 5, 7, 9].

Conclusion

The application of HRW in the sports industry has been rapidly expanding in scope and ubiquity with its presentation as a nutritional supplement. Various randomized controlled, crossover studies support that HRW and other hydrogen-rich applications have antioxidant, anti-inflammatory, and anti-fatigue effects on trained athletes during high-intensity exercise. However, interpretation of the evidence presented is restricted because of methodologic flaws which did not control for confounding variables through crossover studies, potential bias, and inconsistent results. Further, due to the paucity of recent literature on the impact of HRW during exercise, the results of this study should be extrapolated with caution, especially in the field of nutritional medicine. Despite the lack of high-quality clinical investigations in the literature, athletes and coaches have incorporated ingestion of HRW into practice for its anecdotal claims of fatigue resistance and improved endurance. Future high-quality research is needed to further substantiate the antioxidant, anti-inflammatory, anti-fatigue, and performance enhancement effects of HRW.

References

12. Ooi CH, Ng SK, Omar EA. Acute ingestion of hydrogen-rich water does not improve incremental treadmill running performance in endurance-trained athletes. Appl Physiol Nutr Metab. 2020


