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Hydrogen-Rich Water Affected Blood Alkalinity in Physically Active Men

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Possible appliance of effective and safe alkalizing agent in the treatment of metabolic acidosis could be of particular interest to humans experiencing an increase in plasma acidity, such as exercise-induced acidosis. In the present study we tested the hypothesis that the daily oral intake of 2L of hydrogen-rich water (HRW) for 14 days would increase arterial blood alkalinity at baseline and post-exercise as compared with the placebo. This study was a randomized, double blind, placebo-controlled trial involving 52 presumably healthy physically active male volunteers. Twenty-six participants received HRW and 26 a placebo (tap water) for 14 days. Arterial blood pH, partial pressure for carbon dioxide (pCO_2), and bicarbonates were measured at baseline and postexercise at the start (day 0) and at the end of the intervention period (day 14). Intake of HRW significantly increased fasting arterial blood pH by 0.04 (95% confidence interval; 0.01 – 0.08; $p < 0.001$*), and postexercise pH by 0.07 (95% confidence interval; 0.01 – 0.10;* $p = 0.03$*) after 14 days of intervention. Fasting bicarbonates were significantly higher in the HRW trial after the administration regimen as compared with the preadministration (30.5 ± 1.9 mEq/L vs. 28.3 ± 2.3 mEq/L;* $p < 0.0001$*). No volunteers withdrew before the end of the study, and no participant reported any vexatious side effects of supplementation. These results support the hypothesis that HRW administration is safe and may have an alkalizing effect in young physically active men.*

KEYWORDS *bicarbonates, exercise, metabolic acidosis, pH*

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INTRODUCTION

Electrolysis of water produces acidic oxidized water near the anode and alkaline electrolyzed-reduced water (also known as hydrogen-rich water—HRW) near the cathode, with HRW exhibiting a high pH, low dissolved oxygen, high dissolved hydrogen, and significant negative redox potential values (Hanaoka, 2001; Lee, Kim, Ryoo, Lee, & Park, 2006; Shirahata et al., 1997). Although the production of HRW is elemental and a well-established process, the use of HRW in human nutrition is rather new, with HRW highly promoted for drinking purposes in the past 10 years (Huang, Kawamura, Toyoda, & Nakao, 2010). Hydrogen-rich water (HRW) is being marketed as a nutritional aid for humans, accompanied by claims for acidity-lowering, antioxidant, and antiaging effects. These claims extrapolate the findings from animal studies (Fang et al., 2011; Lin et al., 2011; Watanabe et al., 1998), but they have not been substantiated with regard to humans. Specifically, possible appliance of HRW as an alkalizing agent in the treatment of metabolic acidosis could be of particular interest to humans experiencing an increase in plasma acidity. Although rare in the general population, exercise-induced metabolic acidosis is a common metabolic disturbance among physically active individuals (Robergs, Ghiasvand & Parker, 2004). It is characterized by low pH in body tissues and blood accompanied by the build up of lactate and a variety of neuromuscular and cardiorespiratory responses (Cairns, 2006). Exercise-induced metabolic acidosis is a distinct form of metabolic acidosis that typically occurs during vigorous exercise when cells are forced to rely on nonmitochondrial adenosine triphosphate (ATP) turnover that leads to proton release and decrease in serum pH that could negatively affect exercise performance (Robergs et al., 2004). The initial goal for physically active individuals with acidemia is to raise the systemic pH with an alkalizing agent, such as bicarbonates. Although bicarbonate is a popular ergogenic aid used primarily by athletes in short-duration, high-intensity sporting events and competitions, adverse reactions to the administration of sodium bicarbonate (e.g., gastrointestinal distress, metabolic alkalosis, edema due to sodium overload) could limit its use in the treatment of exercise-induced acidosis (McNaughton, Siegler & Midgley, 2008). Therefore, many physically active men and women are looking for an effective dietary agent with an alkalizing effect that does not have side effects (Requena, Zabala, Padial, & Feriche, 2005). As a possible acidity-lowering agent, alkaline HRW could be used by humans to combat the effects of acid produced by exercise (Ostojic, 2012). Yet, to our best knowledge, no previous cross-sectional or longitudinal study has examined the effects of HRW on blood buffering capacity in humans. The main aim of the study was to investigate in a double-blind, placebo-controlled randomized trial, first, whether intake of HRW improved blood alkalinity indicators in young active men and, second, how many participants experienced adverse effects upon follow-up after the treatment. In the

current study we tested the hypothesis that daily oral administration of 2 liters of HRW for 14 days would increase arterial pH at baseline and postexercise, but not increase prevalence of adverse effects as compared with tap water.

MATERIAL AND METHODS

Male athletes requesting a preparticipation medical examination at the Centre of Health, Exercise and Sport Sciences, Belgrade, during September and October 2010, who were experienced in sport training (> 2 years) and who were between 20 and 30 years of age, were recruited for inclusion in the study. Potential candidates were not included in the study if any of the following criteria were present: (1) a history of metabolic disease; (2) musculoskeletal dysfunction; (3) known heart disease; (4) smoking; (5) use of any performance-enhancing drugs or dietary supplements within the past 30 days; (6) an impaired response to exercise test; and (7) residence outside the city of Belgrade, or unwillingness to return for follow-up. Following recruitment, 52 participants met the criteria to participate in the study. All participants were fully informed verbally and in writing about the nature and demands of the study as well as the known health risks. They completed a health history questionnaire and gave their informed consent regarding their voluntary participation in the study. All procedures were performed in accordance with the Declaration of Helsinki, and the study was approved by the local institutional review board (IRB). The study was carried out at the Center of Health, Exercise and Sport Sciences, Belgrade, with study staff who were familiar with the intended interventions. Participants were randomized according to a computer-generated randomization list in a double-blind design to receive either HRW or placebo (tap water) at a dose of 2 liters per day by oral administration for 14 days. NORP Inc. (San Diego, CA, USA) provided both supplement and placebo drinks. The HRW was generated with pulverized magnesium (20 mg) dissolved into 0.5 L of potable water ($Mg + 2H_2O \rightarrow Mg(OH)_2 + H_2$; Ostojic, 2012). Characteristics of administration waters are presented in Table 1, with properties determined by a multiparameter monitor (HQ40D Meter, Hach, Loveland, CO, USA). Both HRW and placebo were administered in coded bottles of 0.5 L that were identical. Both liquids were clear, tasteless, colorless, and odorless.

Participants received either the HRW or placebo drink and self-administered the drink during the study. Four bottles per day were provided, with participants instructed to drink the fluid, sipping throughout the day. The participants were asked to record the quantity of experimental drink taken daily. The code was revealed to the researchers once recruitment, data collection, and laboratory analyses were complete. The primary endpoint with respect to the efficacy in blood buffering was the increase of blood pH achieving a significant change in pH level from baseline to 2 weeks. All

TABLE 1 Characteristics of Administered Waters (Values Are Mean ± SD)

	Placebo (tap water)	Hydrogen-rich water	*p*
Value of pH	7.2 ± 1.1	9.3 ± 0.3	< 0.0001
Oxidation-reduction potential (mV)	300 ± 35	−372 ± 52	< 0.0001
Electric conductivity (ms/m)	9.3 ± 3.1	12.0 ± 1.1	0.0002
Dissolved oxygen (mg/L)	7.1 ± 0.4	6.0 ± 0.3	< 0.0001
Residual chlorine (mg/L)	0.43 ± 0.15	0.12 ± 0.05	< 0.0001

testing was conducted at the baseline and at the end of the second week, and the participants were assessed on the same day, with the tests performed in the same order. Participants were instructed to report any adverse effects of supplementation through an open-ended questionnaire at the end of the intervention. Participants were asked to maintain their usual dietary intake and not to change their physical activity patterns during the study.

Participants visited the laboratory on two occasions: upon the initial intervention and 14 days following the intervention. All measurements were taken between 9 and 11 a.m. after an overnight fast of between 10 and 12 h. The last bottle of fluid was consumed approximately 10 hours before each blood draw. At each of the two visits, participants provided a blood sample from a radial artery into an evacuated test tube while seated, both at baseline and postexercise. After baseline measurements were taken, participants performed in a running test for endurance followed by sampling of postexercise blood. A week before the commencement of the study, the participants performed a familiarization trial on the treadmill. In the 24 hours before the exercise test, the participants did not participate in any prolonged exercise or drink alcoholic, caffeine beverages, or both. The exercise test was performed according to incremental protocol using a treadmill system (Trackmaster TMX425C, Newton, MA, USA). The running protocol consisted of five 3-min workloads with participants beginning at a running speed of 8 km/h and increased by 2 km/h for each subsequent workload. A postexercise blood sample was taken during the first 30 s of recovery. Arterial blood pH was determined by direct method with a Cambridge pH meter equipped with a micro glass electrode (Pye Ltd., Cambridge, UK), and partial pressure for carbon dioxide (pCO_2) was assayed by a NPT7 Blood Gas Analyzer (Radiometer America Inc., Westlake, OH, USA). Serum bicarbonates were analyzed by standard enzymatic methods (Roche Diagnostics Corp., Indianapolis, IN, USA) and an automated analyzer (Hitachi 704, Tokyo, Japan). For all values, the first reading was discarded and the mean of the next three consecutive readings with a coefficient of variation below 15% was used in the study. The data are expressed as means ± SD and were analyzed using the statistical package SPSS, PC program, version 14.0 (SPSS Inc., USA). Baseline characteristics of study participants and percentage change

of acid-base outcomes (0 vs. 2 weeks) between groups were compared with two-sample *t* tests. Mixed-design analysis of variance with repeated measures was used to determine if any significant differences existed between participants' responses over time. When significant differences were found, the Bonferroni post-hoc test was employed to identify the differences. In order to perform the individual responder analysis, participants in the HRW and placebo groups were categorized as responders, partial responders, or nonresponders based on their change in fasting blood pH from the beginning to the end of the study. Because clinically meaningful changes in blood pH have been shown to correspond to an increase of 0.05 (Khanna & Kurtzman, 2000), patients with a $\geq$ 0.05 increase in pH were categorized as responders; those with an increase of between 0.01 and 0.04 were categorized as partial responders; and those with no change or a decrease in pH were categorized as nonresponders. Differences in percentages of participants within each responder group were evaluated using chi square analysis. *P* values of less than or equal to 0.05 were considered to be statistically significant.

RESULTS

No participants withdrew before the end of the study or reported any vexatious side effects of supplementation. Baseline characteristics of participants are presented in Table 2. The baseline data of the groups (HRW vs. placebo) were compared for physical characteristics, and fasting and postexercise blood alkalinity outcomes (e.g., pH, pCO_2, and bicarbonates), with no significant differences found between the groups ($p > 0.05$).

TABLE 2 Baseline Characteristics of Study Participants (Values Are Mean ± SD)

	Placebo ($n = 26$)	Hydrogen-rich water ($n = 26$)	*p*
Age (years)	23.8 ± 4.5	25.1 ± 3.4	0.25
Weight (kg)	79.8 ± 8.4	80.1 ± 7.3	0.89
Height (cm)	180.2 ± 9.1	181.0 ± 8.8	0.75
Body mass index (kg/m^2)	24.6 ± 2.1	24.4 ± 1.9	0.48
Body fat (%)	11.3 ± 4.8	10.9 ± 3.5	0.73
Maximal oxygen uptake (ml/kg/min)	53.5 ± 5.6	52.8 ± 7.2	0.70
Blood pH value			
Fasting	7.40 ± 0.09	7.40 ± 0.07	0.99
Postexercise	7.36 ± 0.13	7.39 ± 0.15	0.45
Partial pressure for carbon dioxide (mm Hg)			
Fasting	41.3 ± 2.6	40.8 ± 8.4	0.77
Postexercise	37.8 ± 4.0	36.2 ± 5.1	0.21
Serum bicarbonates (mEq/L)			
Fasting	27.2 ± 3.7	28.3 ± 2.3	0.21
Postexercise	25.9 ± 3.1	26.5 ± 1.9	0.41

Most participants received all interventions regularly, but a few omitted some quantity of drink. The total compliance with the regimen was 95 ± 3% for the HRW and 96 ± 2% for the placebo group. Percentage changes in arterial blood alkalinity profiles are presented in Figure 1. Results indicated a significant difference between groups for all fasting and post-exercise blood acid-base responses ($p < 0.05$).

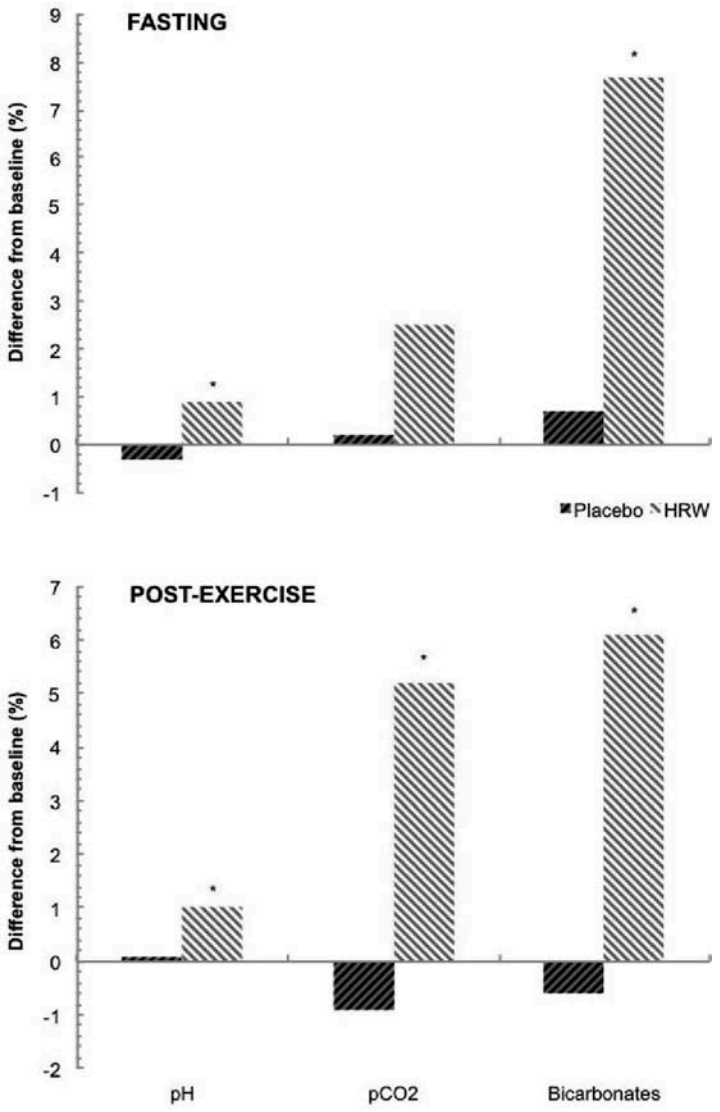

FIGURE 1 Percentage change of acid-base outcomes 0 vs. 2 weeks. HRW denotes hydrogen-rich water, and pCO_2 partial pressure for carbon dioxide in arterial blood. *Indicates significant difference between groups ($p < 0.05$).

TABLE 3 *P* Values for Mixed-Design ANOVA With Repeated Measures

	Time effect	Group effect	Time × group interaction effect
Blood pH			
Fasting	0.19	0.43	0.19
Postexercise	0.02	0.11	0.23
Partial pressure for carbon dioxide			
Fasting	0.97	0.64	0.70
Postexercise	0.60	0.40	0.25
Serum bicarbonates			
Fasting	0.001	0.06	0.11
Postexercise	0.006	0.15	0.10

Fasting arterial blood pH and bicarbonates increased significantly from before to after administration in HRW-supplemented participants ($p < 0.001$). After 2 weeks of administration, the HRW group had higher levels of fasting pH than the placebo group (7.44 ± 0.10 vs. 7.38 ± 0.09, $p = 0.03$) and higher levels of bicarbonates (30.5 ± 1.9 vs. 27.1 ± 1.3 mEq/L, $p < 0.001$). Intake of HRW significantly increased postexercise pH from 7.39 ± 0.15 to 7.46 ± 0.11 ($p = 0.03$) after 2 weeks of intervention. Furthermore, postexercise serum bicarbonates were elevated by 2.5 mEq/L (95% confidence interval; 0.8–4.3), and postexercise pCO_2 elevated by 2.0 mmHg (95% confidence interval; 1.0–3.3) after 2 weeks of administration in HRW trail, respectively. There were no significant differences in arterial blood pH, bicarbonates, and pCO_2 from before to after administration in the placebo group ($p > 0.05$). Repeated measures two-way ANOVA revealed no significant treatment × time interaction effect for fasting and postexercise blood acid-base responses, with significant time effect for postexercise arterial blood pH ($p = 0.02$) and fasting ($p = 0.001$) and postexercise serum bicarbonates ($p = 0.006$), respectively (Table 3).

As shown in Figure 2, significant differences were found between the HRW and placebo groups on the percentage of subjects categorized as responders (30.8% vs. 7.7%), partial responders (50.0% vs. 23.1%), and nonresponders (19.2% vs. 69.2%, respectively, $X^2 = 52.0$, $P < 0.0001$).

DISCUSSION

This study has provided the first direct analysis of the influence of a 2-week HRW oral administration on selected indicators of arterial acid-base profile in young physically active men. The HRW-supplemented group had significant increases in fasting arterial blood pH (0.04) and serum bicarbonates (2.5 μmol/L) as compared with the baseline and had significant increase in postexercise pH (0.07). Fasting blood pH was increased from 0.01 to 0.08 in

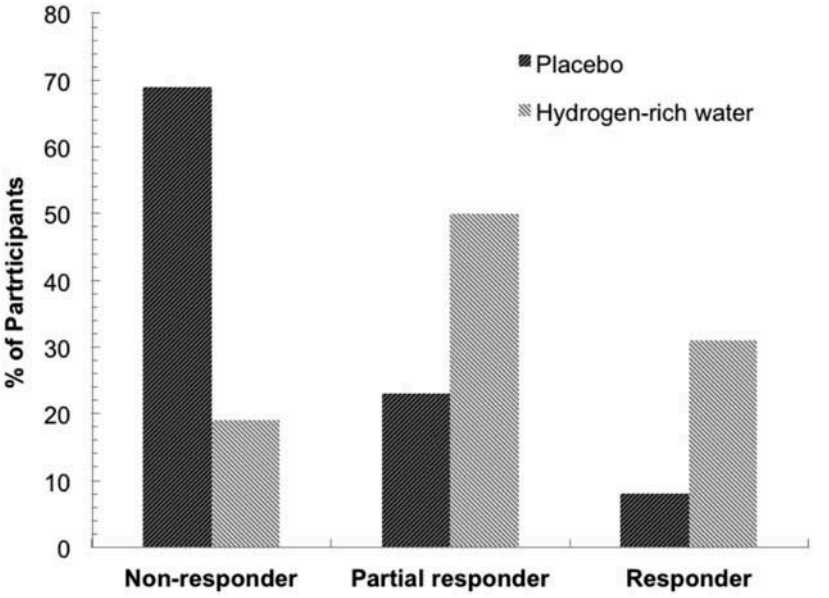

FIGURE 2 Percentage of participants in the HRW ($n = 26$) and placebo ($n = 26$) groups who were categorized as a nonresponder, partial responder, or responder based on their change in fasting blood pH from the beginning to the end of the study.

more than 80% of participants (responders and partial responders) supplemented with HRW. Hydrogen-rich water is considered relatively safe when taken 2 liters per day for 14 days.

Hydrogen water has been used for years by the food industry to sanitize food products (Hricova, Stephan, & Zweifel, 2008). Due to the strong antimicrobial effect in food processing, it has been proposed that hydrogen-rich water could have health benefits if orally administered (Abadias, Usall, Oliveira, Alegre, & Viñas, 2008). Some research suggests that alkaline-reduced water may be useful in scavenging free radicals in the laboratory setting (Hanaoka, 2001; Lee et al., 2006; Shirahata et al., 1997). Several recent studies have investigated the effect of HRW in animals. Among other effects, evidence suggests that hydrogen-rich water may provide some benefits as a neutralizing agent, scavenging active oxygen species in rodents (Kim & Kim, 2006; Lee et al., 2006; Li et al., 2002). In a recent study, Abol-Enein and coworkers examined the effects of ionized alkaline water in dogs and rats with experimentally induced metabolic acidosis (Abol-Enein, Gheith, Barakat, Nour, & Sharaf, 2009). The ionized water-supplemented models had significant improvement of both the partial pressure of carbon dioxide and serum bicarbonate ($p = 0.007$ and 0.001, respectively), with the authors concluding that alkaline-reduced water can be considered as a safe strategy in the management of metabolic acidosis. Yet, only few studies have been published in peer-reviewed journals investigating HRW in humans

(Huang, Yang, Lee, & Chien, 2003; Huang et al., 2006; Nakao, Toyoda, Sharma, Evans, & Guthrie, 2010; Ostojic, 2012), with most of the studies focused on the effect of HRW in reducing hemodialysis-induced oxidative stress in end-stage renal diseases. According to the results of the present study, orally administered HRW significantly increased fasting arterial blood pH and serum bicarbonates. Due to the fact that HRW exhibits high pH, low dissolved oxygen, and extremely high dissolved molecular hydrogen, it seems reasonable that increased non-volatile base indicators in the plasma for the HRW group were due to the ingestion of the alkaline drink. Due to the fact that the intestine is directly involved in acid and/or base generation (Remer, 2001), it appears that HRW has a strong alkalizing effect as a result of absorption of inorganic cations, with the protective mechanism of HRW resulting from active atomic hydrogen with high reductive ability (Hanaoka, 2001). Although nonsignificant, there was also a tendency toward changes in fasting pCO_2 in the HRW trial as compared with baseline at postsupplementation, suggesting compensation of disturbances in the acid-base balance. As such, it could be hypothesized that oral intake of alkaline HRW induces respiratory compensation as the high plasma pH depresses respiration. As a consequence, the pCO_2 is raised and the blood pH tends to fall toward normal. Yet, since the final correction of alkalosis due to ingestion of base is corrected by renal excretion of the excess base, the analysis of the effects of HRW on blood buffering capacity will require assessment of kidney functions (e.g., urine pH, total renal net acid excretion) in prospective studies. Although we examined healthy active men during the present study, the fact that the appropriate treatment of acute metabolic acidosis has been very controversial (Abol-Enein et al., 2009; Huang et al., 2003, 2006) enhances further studies with HRW as a potential antiacidic treatment strategy and its safe application in clinical patients.

During near-maximal exercise efforts lasting more than approximately 60 seconds, muscles rely on ATP that is supplied from nonmitochondrial sources, which increases proton release and causes the acidosis accompanied with lactate production. The drop of muscle pH as a result of proton accumulation is thought to inhibit the resynthesis of ATP as well as inhibit muscle contraction and induce fatigue (Robergs et al., 2004). Several buffering agents could increase the body's capacity to neutralize accumulated acid, thereby delaying fatigue during high-intensity exercise (McNaughton et al., 2008; Requena et al., 2005). Yet, its use is often limited by different adverse events, with overall incidence of significant side effects after bicarbonates administration of about 25% (Kaehny & Anderson, 1994). According to the results of the present study, HRW increases arterial blood pH levels and elevated serum bicarbonates sampled 30 seconds after an endurance exercise test, making blood less acidic as compared with placebo. Higher postexercise pH in an HRW trial possibly indicates a better environment for repeated muscle contraction, and it could be assumed that HRW buffers inorganic

cations generated by exercise by its alkalinity potential. Since we did not assess exercise performance indicators (e.g., power output), it is not clear if HRW is an effective sports ergogenic.

Since we had controlled and comparable conditions for all participants during the study and a double-blind, placebo-controlled design with the subjects clear of a vitamin supplementation regimen, it is apparent that HRW ingestion had blood buffering effect on the experimental group in the present study. Still, despite these strengths, the study is not without limitations. First, we did not evaluate the possible factors that could affect HRW utilization after oral intake. These could include HRW bioavailability, pharmacokinetics, and biotransformation. Second, the size of the experimental samples could be considered partly limited. Consequently, although seemingly different, the observed differences for time × group interaction effect for some outcomes (e.g., fasting and postexercise serum bicarbonates) could not reach the statistically significant level. Third, we partially controlled some of the extraneous factors that could affect blood alkalinity levels over 2 weeks, such as nutrition and physical activity, yet calculation of alkalies consumed from food sources was not conducted for the present study; neither volumenor intensity of exercise was monitored. During this study we assessed only a few important key components of a blood buffering system neglecting further parameters (e.g., ammonia, inorganic cations, proteins) that are or might be directly or indirectly connected to acid-based homeostasis after HRW administration. Finally, the study may have benefited from three groups design, with an experimental group, placebo-controlled, and a nonexercising control group, which was not possible for the current study due to limited recruitment capacity for nonexercising healthy adults.

The potential health implications of HRW supplementation in humans could be related to an increased ability to sustain or reduce metabolic acidosis (e.g., exercise-induced acidosis), but this possibility needs further scientific confirmation and ethical considerations in studying HRW safety. Caution should be used before recommending HRW, since the long-term health effects of HWR are not known. Previous studies reported no adverse events after short-term HRW administration in humans, with no effects on liver function and hematology indices (Kang et al., 2011; Ohno, Ito, Ichihara, & Ito, 2012). Due to the fact that no participant reported any acute side effects of intervention in the present study, HRW could be considered relatively safe when taken 2 liters per day for 14 days. Yet precaution is obligatory since potential harmful alkalosis due to overconsumption of HRW is not examined so far. Future studies should focus on different dosages and duration of HRW ingestion, with assessment of relevant pharmacodynamic outcomes (e.g., dose-response curve) to further elucidate the safety and efficiency of this new drink.

In conclusion, intake of HRW for 2 weeks appears to increase fasting and postexercise arterial blood pH and bicarbonates, with no significant adverse effects. Hydrogen-rich water (HRW) acts as an alkalizing agent,

probably due to high content of anions and high reductive ability. These early findings are promising regarding potential application of HRW as an alkalizing agent in both physically actives and nonathletic individuals. Future studies should be undertaken to fully understand the scavenging potential of alkaline water in humans.

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