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Research

Effects of 12-Week Hydrogen-Rich Water Consumption on Body Composition and Metabolic Biomarkers in Adults with Metabolic Syndrome Stratified by Breath Hydrogen Levels: A Randomized Controlled Trial

[1,2]Nikola Todorovic, [1]David Nedeljkovic, [1]Darinka Korovljev, [1]Milos Obrenovic, [3]Laszlo Ratgeber, [3]Jozsef Betlehem, [3]Viktoria Premusz, [3]Pongrac Acs, [4]Alex Tarnava, [1,3]Sergej M. Ostojic

[1] *Applied Bioenergetics Laboratory, Center for Mitochondrial Medicine, Medical Polyclinic Fizikus, Belgrade, Serbia;*
[2] *Faculty of Sport, University of Ljubljana, Ljubljana, Slovenia;*
[3] *Faculty of Health Sciences, University of Pécs, Pécs, Hungary;*
[4] *Natural Wellness Now Health Products Inc., Maple Ridge, BC, Canada*

Metabolic syndrome is a cluster of risk factors that increases the likelihood of cardiovascular disease and type 2 diabetes. Hydrogen-rich water (HRW) has been proposed as a nutritional strategy to improve metabolic health, although individual differences in endogenous hydrogen production may influence its effectiveness. In this randomized, double-blind, placebo-controlled trial, 40 adults with metabolic syndrome (mean age 51.2 ± 7.9 years; 27 women) were assigned to consume 1,000 mL/day of HRW or placebo for 12 weeks. Baseline breath hydrogen levels stratified participants into low (< 10 ppm) or high (≥ 10 ppm) hydrogen groups. Anthropometric, body composition, and metabolic biomarkers were assessed at baseline and post-intervention, with change in waist circumference as the primary outcome. HRW supplementation led to significant improvements in body weight, BMI, waist circumference, fat mass, fat-free mass, muscle mass, and total body water compared with placebo ($P \leq 0.05$), with large effect sizes observed for reductions in waist circumference. Significant improvements were also noted in fasting glucose, lipid profile, apolipoproteins A and B, and high-sensitivity C-reactive protein ($P \leq 0.05$). Treatment effects were generally more pronounced in participants with lower baseline breath hydrogen levels. No major adverse events were reported. These findings indicate that HRW supplementation safely improves multiple components of metabolic syndrome, with greater benefits observed in individuals with lower endogenous hydrogen production, supporting its potential role as a personalized adjunctive intervention.

Keywords: hydrogen · metabolic syndrome · body composition · lipid profile · clinical trial.

Abbreviations Used: None

Corresponding Author: Professor Sergej M. Ostojic, MD, PhD, ORCID ID: http://orcid.org/0000-0002-7270-2541, E-mail addresses: sergej.ostojic@chess.edu.rs and sergej.ostojic@etk.pte.hu

INTRODUCTION

Metabolic syndrome is a constellation of interrelated cardiometabolic risk factors that collectively increase the risk of developing cardiovascular disease, type 2 diabetes mellitus, and all-cause mortality (Swarup et al., 2025). It is typically defined by the co-occurrence of central (abdominal) obesity, insulin resistance, elevated blood pressure, atherogenic dyslipidemia—characterized by elevated triglyceride levels and reduced high-density lipoprotein (HDL) cholesterol—and impaired glucose homeostasis. The global prevalence of metabolic syndrome is steadily rising, currently affecting an estimated 20–25% of the adult population. This burden is particularly pronounced among older individuals, as well as those with sedentary lifestyles and poor dietary habits (International Diabetes Federation, 2006; Pigeot & Ahrens, 2025).

The syndrome poses a substantial public health challenge due to its association with increased healthcare utilization, reduced workplace productivity, and diminished quality of life (Cicekli et al., 2023). Moreover, metabolic syndrome is strongly linked to a range of comorbid conditions, including non-alcoholic fatty liver disease, polycystic ovary syndrome, chronic kidney disease, and several types of malignancies (Lam et al., 2019). While early diagnosis and effective management—primarily via lifestyle interventions and, where necessary, pharmacotherapy—are essential to prevent long-

term complications, growing attention has been directed toward adjunctive nutritional strategies.

Among such approaches, hydrogen-rich water (HRW) has recently garnered interest as a potential intervention for mitigating metabolic dysfunction. Although findings on the efficacy of various dietary strategies remain mixed (Castro-Barquero et al., 2020), several preclinical and clinical studies have demonstrated promising effects of HRW in improving metabolic parameters, including lipid profiles, glucose metabolism, and markers of oxidative stress in individuals with metabolic syndrome and/or obesity (Nakao et al., 2010; Song et al., 2013; LeBaron et al., 2020; Chiu et al., 2023; Korovljev et al., 2023a; Moribe et al., 2024). A recent systematic review and meta-analysis further supports these findings, showing that HRW consumption significantly improves lipid status in clinical populations, including those with metabolic syndrome (Todorovic et al., 2023).

Importantly, hydrogen gas can also be produced endogenously by gut microbiota through fermentation processes in the colon (Campbell et al., 2023). Therefore, the effectiveness of exogenously administered HRW may be influenced by an individual's baseline endogenous hydrogen production. Based on this premise, the primary objective of the present randomized controlled trial was to assess the effects of HRW supplementation on body composition and key metabolic biomarkers in adults with metabolic syndrome, stratified by baseline breath hydrogen levels. We hypothesized that individuals with lower baseline breath hydrogen concentrations would exhibit greater metabolic improvements in response to HRW compared to those with higher endogenous hydrogen production, suggesting a potential compensatory benefit of exogenous hydrogen intake in this subgroup.

METHODS

Participants

This study was conducted as a randomized, double-blind, placebo-controlled, parallel-group interventional trial. Eligible participants were randomly assigned to one of four intervention arms based on their baseline breath hydrogen levels and treatment allocation: Experimental Group 1 (EXP1; low breath hydrogen; receiving HRW), Experimental Group 2 (EXP2; high breath hydrogen; receiving HRW), Control Group 1 (CON1; low breath hydrogen; receiving placebo), and Control Group 2 (CON2; high breath hydrogen; receiving placebo). Participants were adults aged 30 to 65 years diagnosed with metabolic syndrome, defined by the presence of at least three out of the following four criteria: waist circumference ≥ 102 cm in men or ≥ 88 cm in women; elevated triglycerides (≥ 1.695 mmol/L); reduced HDL cholesterol (< 1.04 mmol/L in men or < 1.30 mmol/L in women); elevated blood pressure (> 130/85 mmHg); and elevated fasting glucose (> 6.1 mmol/L). Additional inclusion criteria included a sedentary lifestyle and the provision of written informed consent. Exclusion criteria comprised the use of dietary supplements within four weeks prior to the intervention, presence of major chronic disease or acute injury, recent use (within four weeks) of metabolism-modulating pharmacological agents, refusal to undergo randomization, or participation in other concurrent clinical trials. Prior to enrollment, all participants underwent a comprehensive health screening that included a detailed medical history review, physical examination, and baseline laboratory assessments, including measurement of breath hydrogen levels. Molecular hydrogen levels in breath were measured using an electrochemical fuel cell microprocessor (LactoFAN2, Fischer Analysen Instrumente GmbH, Leipzig, Germany). A threshold value of 10 parts per million (ppm) was established to stratify participants based on endogenous hydrogen production. Individuals with breath hydrogen levels below 10 ppm were classified into the low-breath hydrogen groups, whereas those with levels equal to or exceeding this threshold were assigned to the high-breath hydrogen groups. Written informed consent was obtained from all individuals prior to their inclusion in the study. The study protocol was approved by the local Institutional Review Board (Approval No. 51-02-01/2025-1) and conducted in accordance with the ethical principles outlined in the 7th revision of the Declaration of Helsinki. The trial was prospectively registered on ClinicalTrials.gov (Identifier: NCT06968715); the study was registered while the corresponding author was affiliated with the University of Novi Sad.

Experimental intervention

Participants assigned to the experimental groups consumed 1,000 mL of HRW daily, while those in the control groups received an equivalent volume of placebo water. HRW was prepared by dissolving a single HRW tablet in a cup of tap water (330 mL), generating hydrogen gas through the reaction: $Mg + H_2O \rightarrow H_2 + Mg(OH)_2$. Each HRW serving contained approximately 5 mg of dissolved molecular hydrogen, whereas the placebo contained none. Both HRW and placebo tablets were manufactured and supplied by Natural Wellness Now Health Products Inc. (Maple Ridge, BC, Canada). The tablets were identical in appearance, texture, and sensory characteristics, and were standardized for magnesium content (80 mg per serving) to preserve the study blinding. The intervention was administered as a beverage in three daily servings, taken in the morning, early afternoon, and before dinner. To reduce potential interference from carbohydrate metabolism, participants were instructed to consume each serving at least two hours after a carbohydrate-containing meal. The study maintained a double-blind design, with both participants and research personnel unaware of group assignments. Randomization and treatment allocation were performed by an independent technician not involved in any other aspect of the study or data analysis. The intervention period lasted twelve weeks, during which participants were asked to refrain from using any additional dietary supplements or weight management products.

Study outcomes

Prespecified outcome measures included anthropometric parameters, body composition, resting blood pressure, biochemical markers, and the incidence and severity of adverse effects. All outcomes were assessed at two time points: baseline (pre-intervention) and following 12 weeks of supplementation (post-intervention). The primary outcome was the change in waist circumference from baseline to the end of the intervention period. All lab assessments were conducted between 08:00 and 12:00 following an overnight fast of at least 10 hours. Anthropometric measurements included height (Seca 210, Hamburg, Germany) and body weight (Omron BF508, Tokyo, Japan), with body mass index (BMI) calculated as weight in kilograms divided by height in meters squared (kg/m^2). Waist circumference was measured using a non-elastic anthropometric tape (Gulick CHP, Ann Arbor, MI) at the midpoint between the lowest rib and the iliac crest. Body composition, including fat mass, fat-free mass, muscle mass, and total body water, was assessed using a multifrequency bioelectrical impedance analyzer (BioScan 920, Maltron International Ltd., Rayleigh, UK). Resting blood pressure was measured in triplicate using an automated oscillometric monitor (Omron 3, Tokyo, Japan), following a 5-minute seated rest, and the average of the final two readings was recorded. Fasting blood

samples were collected from the antecubital vein using serum separator gel vacutainers and centrifuged at 3,000 × g for 10 minutes. Serum aliquots were stored at –80°C until biochemical and safety analyses were performed. Glucose, total cholesterol, triglycerides, and lipoprotein levels were quantified using standard enzymatic assays with an automated analyzer (Hitachi, Tokyo, Japan). Additional biomarkers, including lipoprotein(a), apolipoprotein A (APO-A), apolipoprotein B (APO-B), total antioxidant capacity (TAC), superoxide dismutase (SOD), glutathione, and high-sensitivity C-reactive protein (hs-CRP), were measured using commercially available ELISA kits (Elabscience, Houston, TX, USA). Adverse events, including gastrointestinal disturbances and systemic symptoms, were monitored through open-ended self-report questionnaires. Participants were withdrawn from the trial if they experienced severe gastrointestinal or systemic side effects (e.g., nausea, vomiting, diarrhea, headache, palpitations, fatigue, fever) or other significant health changes deemed unrelated to the intervention. Compliance was assessed at each follow-up visit by counting the number of returned intervention units, with adherence defined as consumption of at least 75% of the prescribed doses. Participants received detailed verbal and written instructions at the initial visit, and weekly follow-up telephone calls were conducted to reinforce adherence and address concerns. To ensure consistency, all assessments were conducted in a standardized sequence on the same day for each participant.

Statistical analyses

The minimum required sample size (n = 36) was determined a priori using G*Power 3.1 software (Heinrich Heine University Düsseldorf, Germany). The calculation was based on an expected small effect size (Cohen's d = 0.30), an alpha level of 0.05, and a statistical power of 0.80, assuming changes in waist circumference as the primary outcome from baseline to the 12-week follow-up. The analysis incorporated a parallel-group design with four intervention arms and two repeated measurement points (baseline and post-intervention). To account for potential attrition and ensure adequate power, the sample size was increased to 40 participants. To promote balance in participant characteristics across groups, stratified randomization was employed, with gender (male and female) used as a stratification factor. Data were tested for normality using the Shapiro–Wilk test, while the homogeneity of variances was assessed using Bartlett's test. Within-group changes from baseline to post-intervention were analyzed using paired t-tests for normally distributed variables and the Wilcoxon Signed-Rank Test for non-normally distributed variables. For variables meeting the assumptions of normality and homogeneity of variance, interaction effects between time and intervention group were assessed using a two-way mixed model ANOVA. When the assumption of homogeneity of variance was violated, the non-parametric Friedman test was applied as an alternative for repeated measures. Statistical significance was set at $P \leq 0.05$. Post-intervention effect sizes were calculated using Cohen's d, with thresholds for interpretation defined as small (d = 0.2), medium (d = 0.5), and large (d = 0.8) effects. Missing data were handled using multiple imputation by chained equations (MICE), implemented via the IterativeImputer function from Pedregosa et al. (2011). All statistical analyses were conducted using IBM SPSS Statistics for Mac, version 24.0 (IBM Corp., Armonk, NY, USA).

RESULTS

A total of 40 participants (mean age: 51.2 ± 7.9 years; 27 females) were enrolled in the study and randomly allocated to the intervention arms, with ten participants assigned to each group. A total of 35 participants received their allocated supplementation in accordance with the study protocol, completed the intervention, and were included in the primary outcome analysis. Five participants were lost to follow-up for reasons unrelated to the study. The flow of participants through each stage of the randomized crossover trial is depicted in the CONSORT diagram (Figure 1).

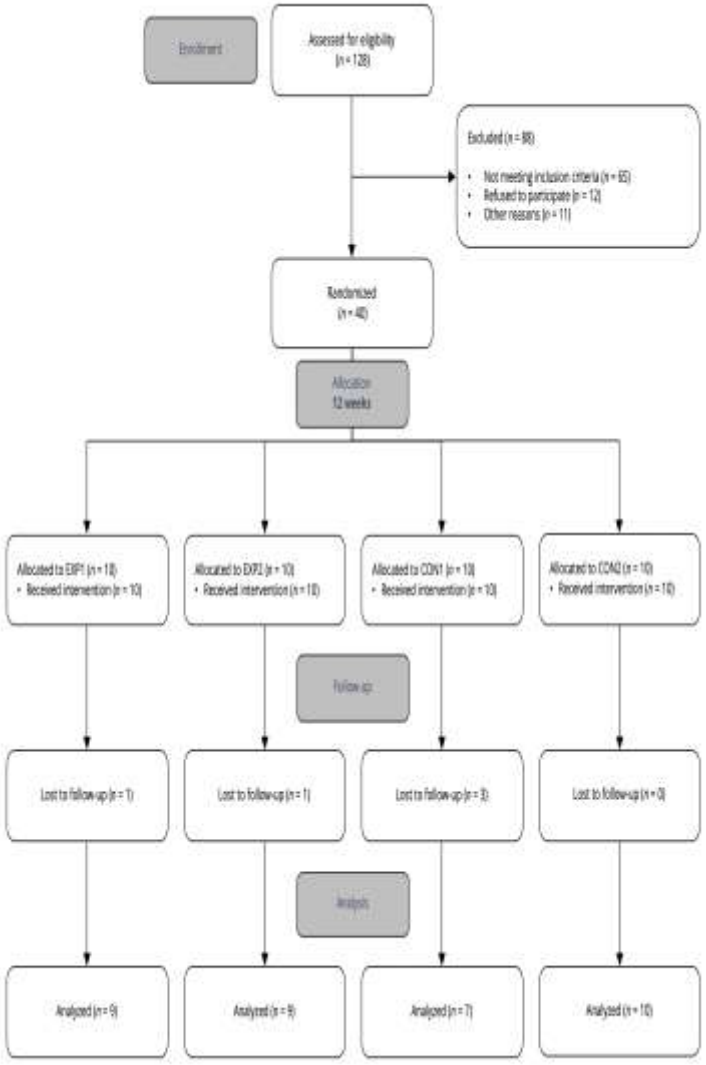

Figure 1. Flow diagram depicting participants flow throughout the study. EXP1, low-breath hydrogen receiving hydrogen-rich water; EXP2, high-breath hydrogen receiving hydrogen-rich water; CON1, low-breath hydrogen receiving placebo; CON2, high-breath hydrogen receiving placebo.

Changes in the primary and secondary outcomes over the course of the trial are presented in the subsequent tables. Table 1 summarizes the variations in anthropometric parameters (including body weight, BMI, and waist circumference), body composition indices (such as fat mass, fat-free mass, muscle mass, and total body water),as well as resting heart rate and blood pressure measurements recorded at baseline and post-intervention. Table 2 provides a detailed overview of the changes in biochemical markers, encompassing lipid profile, glucose, and other relevant metabolic indicators assessed as part of the study protocol.

Table 1. Anthropometric and physiological indices at baseline and at 12-week follow-up across groups. Values are presented as mean ± SD.

	Group	Baseline	Follow-up	Delta	*d*	*P*	Post-hoc
Weight (kg)	EXP1	87.5 ± 12.7	86.1 ± 12.6 *	-1.4 ± 1.0	1.43	0.05	^{bcde}
	EXP2	82.8 ± 10.9	80.9 ± 10.4 *	-1.9 ± 1.4	1.38		
	CON1	88.2 ± 13.7	87.9 ± 13.8 *	-0.3 ± 0.3	0.89		
	CON2	86.5 ± 19.1	86.3 ± 19.0	-0.2 ± 0.3	0.51		
Body mass index (kg/m^2)	EXP1	29.9 ± 5.5	29.5 ± 5.5 *	-0.5 ± 0.3	1.51	0.05	^{bcde}
	EXP2	29.1 ± 4.7	28.4 ± 4.6 *	-0.7 ± 0.5	1.39		
	CON1	31.5 ± 5.9	31.4 ± 5.9 *	-0.1 ± 0.1	0.87		
	CON2	30.3 ± 6.7	30.3 ± 6.7	-0.1 ± 0.1	0.49		
Waist circumference (cm)	EXP1	103.7 ± 6.9	101.5 ± 7.2 *	-2.2 ± 1.8	1.77	0.02	^{bcde}
	EXP2	107.8 ± 9.0	105.3 ± 9.3 *	-2.4 ± 2.0	1.33		
	CON1	105.5 ± 7.2	105.1 ± 7.4 *	-0.4 ± 0.5	0.70		
	CON2	112.7 ± 7.8	112.4 ± 7.7 *	-0.3 ± 0.4	1.27		
Fat mass (kg)	EXP1	28.6 ± 4.6	27.3 ± 4.1 *	-1.2 ± 0.7	1.30	< 0.01	^{bcde}
	EXP2	30.2 ± 3.2	29.1 ± 3.4 *	-1.1 ± 0.8	1.24		
	CON1	31.8 ± 5.9	31.7 ± 5.9 *	-0.2 ± 0.3	0.68		
	CON2	29.5 ± 6.9	29.2 ± 7.0 *	-0.4 ± 0.3	0.71		
Fat free mass (kg)	EXP1	59.0 ± 8.7	59.6 ± 10.4 *	0.6 ± 05	1.30	< 0.01	^{bcde}
	EXP2	52.7 ± 8.7	53.3 ± 8.7 *	0.6 ± 0.5	1.24		
	CON1	56.3 ± 8.1	56.5 ± 8.0	0.1 ± 0.2	0.68		
	CON2	56.9 ± 14.6	57.1 ± 14.5 *	0.2 ± 0.2	0.71		
Muscle mass (kg)	EXP1	44.0 ± 6.7	44.6 ± 6.8 *	0.6 ± 0.3	2.19	< 0.01	^{bcde}
	EXP2	39.5 ± 6.8	40.1 ± 7.0 *	0.6 ± 0.4	1.57		
	CON1	41.9 ± 7.3	41.9 ± 7.3	0.0 ± 0.2	0.18		
	CON2	43.5 ± 12.2	43.6 ± 12.2	0.1 ± 0,2	0.67		
Total body water (L)	EXP1	35.4 ± 7.0	35.8 ± 6.9 *	0.5 ± 0.4	1.36	0.01	^{bcde}
	EXP2	32.2 ± 6.1	33.0 ± 6.0 *	0.8 ± 0.4	2.05		
	CON1	34.1 ± 3.3	34.3 ± 3.4 *	0.2 ± 0.2	0.89		
	CON2	34.9 ± 10.3	35.0 ± 10.3	0.1 ± 0.2	0.23		
Resting heart rate (bpm)	EXP1	82 ± 10	79 ± 11 *	-3 ± 2	1.29	0.01	^{bcde}
	EXP2	77 ± 7	74 ± 6 *	-3 ± 1	2.10		
	CON1	79 ± 6	78 ± 6	-1 ± 2	0.29		
	CON2	78 ± 8	77 ± 8	-1 ± 1	0.50		
Systolic blood pressure (mm Hg)	EXP1	135 ± 9	130 ± 10 *	-5 ± 4	1.11	0.12	-
	EXP2	133 ± 10	126 ± 11 *	-6 ± 4	1.56		
	CON1	138 ± 13	136 ± 13 *	-2 ± 2	0.82		
	CON2	134 ± 12	133 ± 14	-1 ± 3	0.20		
Diastolic blood pressure (mm Hg)	EXP1	89 ± 9	85 ± 10 *	-4 ± 3	1.30	0.11	-
	EXP2	85 ± 7	80 ± 7 *	-4 ± 3	1.42		
	CON1	86 ± 5	86 ± 6	-1 ± 2	0.52		
	CON2	89 ± 10	88 ± 11	-1 ± 2	0.42		

Abbreviations. EXP1, low breath hydrogen receiving hydrogen-rich water; EXP2, high breath hydrogen receiving hydrogen-rich water; CON1, low breath hydrogen receiving placebo; CON2, high breath hydrogen receiving placebo. Asterisk (*) indicates statistical significance at $P \leq 0.05$ within-group comparison versus baseline levels. *P* indicates the statistical significance of the interaction effect (time × treatment), with superscript letters denote statistically significant differences between individual sample pairs at $P \leq 0.05$ for post-hoc analysis, as follows: ^{b}, EXP1 *vs*. CON1; ^{c} EXP1 *vs*. CON2; ^{d} EXP2 *vs*. CON1; ^{e} EXP2 *vs*. CON2

All anthropometric, body composition, and physiological indices showed statistically significant improvements in both EXP1 and EXP2 groups at the 12-week follow-up ($P \leq 0.05$). In contrast, the control groups generally exhibited stable values throughout the study period. However, in CON1, significant reductions were observed in body weight, BMI, waist circumference, fat mass, and systolic blood pressure, accompanied by an increase in total body water ($P \leq 0.05$). In CON2, significant reductions in waist circumference and fat mass were detected, alongside an increase in fat-free mass ($P \leq 0.05$).

A significant time × treatment interaction was observed for all anthropometric and body composition indices assessed ($P \leq 0.05$), indicating that the magnitude of change over time differed across intervention groups. Both experimental interventions were significantly more effective than their respective placebo counterparts in reducing body weight, BMI, waist circumference, and fat mass, as well as in increasing fat-free mass, muscle mass, and total body water ($P \leq 0.05$). No significant differences in effect sizes were

found between the two experimental interventions. Additionally, a significant time × treatment interaction was detected for resting heart rate (P = 0.02), suggesting that the experimental treatments were more effective than the control conditions in lowering resting heart rate. No significant group differences were observed in the effects on blood pressure (P > 0.05). Notably, the effect sizes for the primary outcome—change in waist circumference—exceeded the conventional threshold for a large effect (d > 0.80) for both experimental interventions. The EXP1 group demonstrated a very large effect (d = 1.77), while the EXP2 group showed a large effect (d = 1.33), indicating that both interventions produced substantial reductions in waist circumference, with EXP1 yielding a more pronounced impact.

Table 2. Biochemical markers at baseline and at 12-week follow-up across groups. Values are presented as mean ± SD.

	Group	Baseline	Follow-up	Delta	*d*	*P*	Post-hoc
Glucose (mmol/L)	EXP1	6.9 ± 0.4	6.8 ± 0.4 *	-0.1 ± 0.1	1.43	< 0.01	*bcde*
	EXP2	6.8 ± 0.3	6.6 ± 0.3 *	-0.2 ± 0.1	2.30		
	CON1	7.0 ± 0.5	7.1 ± 0.5	0.1 ± 0.2	0.45		
	CON2	6.9 ± 0.3	7.0 ± 0.4 *	0.1 _0 0.1	0.73		
Total cholesterol (mmol/L)	EXP1	6.1 ± 0.3	5.9 ± 0.3 *	-0.2 ± 0.1	1.68	0.12	-
	EXP2	5.9 ± 0.6	5.7 ± 0.6 *	-0.2 ± 0.1	1.37		
	CON1	6.1 ± 0.4	6.1 ± 0.4	-0.1 ± 0.1	0.49		
	CON2	6.1 ± 0.6	6.2 ± 0.6	0.0 ± 0.2	0.10		
LDL cholesterol (mmol/L)	EXP1	3.8 ± 0.5	3.5 ± 0.6 *	-0.2 ± 0.2	1.06	< 0.01	*bcde*
	EXP2	3.7 ± 0.3	3.5 ± 0.4 *	-0.2 ± 0.2	1.04		
	CON1	3.9 ± 0.5	4.0 ± 0.4 *	0.1 ± 0.1	1.05		
	CON2	3.7 ± 0.4	3.7 ± 0.3	0.0 ± 0.1	0.18		
HDL cholesterol (mmol/L)	EXP1	1.0 ± 0.1	0.8 ± 0.1 *	-0.2 ± 0.1	2.06	< 0.01	*bcde*
	EXP2	0.9 ± 0.1	0.8 ± 0.2 *	-0.2 ± 0.1	1.27		
	CON1	1.0 ± 0.1	1.0 ± 0.1	0.0 ± 0.1	0.49		
	CON2	0.9 ± 0.1	1.0 ± 0.2	0.0 ± 0.1	0.22		
Triglycerides (mmol/L)	EXP1	2.1 ±0.4	1.9 ± 0.4 *	-0.2 ± 0.1	1.64	< 0.01	*bcde*
	EXP2	2.2 ± 0.3	2.0 ± 0.3 *	-0.2 ± 0.1	2.74		
	CON1	2.1 ± 0.3	2.1 ± 0.3	0.0 ± 0.1	0.36		
	CON2	2.2 ± 0.4	2.3 ± 0.4 *	0.1 ± 0.1	0.76		
Lipoprotein(a) (mg/dL)	EXP1	29.2 ± 10.3	27.9 ± 10.5	-1.2 ± 1.9	0.66	0.27	-
	EXP2	31.4 ± 6.8	31.0 ± 7.3	-0.3 ± 2.1	0.16		
	CON1	34.2 ± 9.7	34.1 ± 9.2	-0.1 ± 1.4	0.09		
	CON2	30.8 ± 8.6	31.1 ± 9.1	0.3 ± 0.9	0.29		
APO-A (g/L)	EXP1	1.2 ± 0.1	1.0 ± 0.2 *	-0.2 ± 0.1	1.43	< 0.01	*bcde*
	EXP2	1.2 ± 0.2	1.1 ± 0.3 *	-0.1 ± 0.1	1.26		
	CON1	1.2 ± 0.1	1.3 ± 0.2	0.1 ± 0.2	0.42		
	CON2	1.2 ± 0.1	1.3 ± 0.1	0.0 ± 0.1	0.53		
APO-B (g/L)	EXP1	1.3 ± 0.1	1.1 ± 0.2 *	-0.2 ± 0.1	1.38	< 0.01	*bcde*
	EXP2	1.2 ± 0.1	1.0 ± 0.1 *	-0.2 ± 0.1	1.68		
	CON1	1.2 ± 0.1	1.3 ± 0.1 *	0.1 ± 0.1	0.64		
	CON2	1.2 ± 0.1	1.2 ± 0.1	0.1 ± 0.1	0.48		
TAC (mmol Trolox equiv./L)	EXP1	1.2 ± 0.2	1.0 ± 0.3 *	-0.2 ± 0.1	1.41	0.01	*bcde*
	EXP2	1.4 ± 0.2	1.2 ± 0.3 *	-0.2 ± 0.1	1.57		
	CON1	1.3 ± 0.2	1.4 ± 0.3 *	0.1 ± 0.1	0.87		
	CON2	1.3 ± 0.1	1.4 ± 0.1	0.1 ± 0.1	0.63		
SOD (U/mL)	EXP1	161.9 ± 21.4	162.4 ± 21.0	0.5 ± 3.2	0.16	0.32	-
	EXP2	163.9 ± 12.4	163.3 ± 10.6	-0.5 ± 3.1	0.18		
	CON1	160.0 ± 17.6	158.3 ± 19.0	-1.8 ± 2.9	0.62		
	CON2	155.2 ± 22.0	154.1 ± 22.1	-1.1 ± 2.9	0.38		
Glutathione (µmol/L)	EXP1	4.0 ± 0.7	3.8 ± 0.6 *	-0.2 ± 0.1	1.40	0.01	*bcde*
	EXP2	4.3 ± 0.4	4.0 ± 0.5 *	-0.2 ± 0.2	1.21		
	CON1	4.0 ± 0.6	4.0 ± 0.6	0.0 ± 0.1	0.03		
	CON2	4.1 ± 0.5	4.1 ± 0.5	0.0 ± 0.1	0.08		
hs-CRP (mg/L)	EXP1	3.5 ± 1.0	3.2 ± 0.9 *	-0.3 ± 0.2	1.75	< 0.01	*bcde*
	EXP2	3.9 ± 1.1	3.6 ± 1.0 *	-0.3 ± 0.2	1.58		
	CON1	3.3 ± 0.8	3.4 ± 0.8 *	0.1 ± 0.1	0.97		
	CON2	3.5 ± 1.2	3.5 ± 1.3	0.0 ± 0.1	0.18		

Abbreviations. EXP1, low breath hydrogen receiving hydrogen-rich water; EXP2, high breath hydrogen receiving hydrogen-rich water; CON1, low breath hydrogen receiving placebo; CON2, high breath hydrogen receiving placebo; LDL, low-density lipoprotein; HDL, high-density lipoprotein, APO, apolipoprotein, TAC, total antioxidant capacity; SOD, superoxide dismutase; hs-CRP, high-sensitive C-reactive protein. Asterisk (*) indicates statistical significance at $P \leq 0.05$ within-group comparison versus baseline levels. *P* indicates the statistical significance of the interaction effect (time × treatment), with superscript letters denote statistically significant differences between individual sample pairs at $P \leq 0.05$ for post-hoc analysis, as follows: [b], EXP1 *vs*. CON1; [c] EXP1 *vs*. CON2; [d] EXP2 *vs*. CON1; [e] EXP2 *vs*. CON2.

At the 12-week follow-up, all evaluated biomarkers demonstrated statistically significant changes in both EXP1 and EXP2 groups ($P \leq 0.05$), except lipoprotein(a) and SOD, which remained unchanged. In contrast, the control groups generally exhibited stable biomarker profiles over the study period. Notable exceptions were observed in CON1, with significant increases in LDL cholesterol, APO-B, TAC, and hs-CRP ($P \leq 0.05$). In CON2, a significant increase in triglyceride levels was observed ($P \leq 0.05$). A significant time-by-treatment interaction was observed for most biochemical markers assessed ($P \leq 0.05$), except for total cholesterol, lipoprotein(a), and SOD, which did not show significant interaction. Both experimental interventions were significantly more effective than their respective placebo controls in reducing concentrations of glucose, LDL and HDL cholesterol, triglycerides, APO-A and APO-B, glutathione, and hs-CRP, as well as in decreasing TAC ($P \leq 0.05$). No statistically significant differences in effect sizes were observed between the two experimental groups.

All participants who completed the trial reported no severe adverse events that interfered with their continued participation. Moreover, no significant alterations in safety biomarkers were observed in any intervention group throughout the study period, and no clinically relevant abnormalities were detected. Within the EXP2 group, one participant (male, 49 years) experienced mild and transient diarrhea during the initial week of intervention, another participant (female, 54 years) reported increased energy levels, and a third participant (female, 53 years) noted a reduction in dizziness. In the CON2 group, one participant (male, 50 years) reported an episode of evening dizziness and food cravings, while another (female, 30 years) experienced mild weakness. Compliance with the intervention protocol was high across all groups, with a mean adherence rate of 92.0 ± 6.5%, and no significant differences in adherence were observed between groups.

DISCUSSION

This randomized, double-blind, placebo-controlled trial investigated the effects of daily HRW supplementation over 12 weeks on body composition and metabolic biomarkers in adults diagnosed with metabolic syndrome, stratified by baseline breath hydrogen levels. The findings provide compelling evidence that HRW exerts beneficial effects on multiple components of the metabolic syndrome phenotype, particularly in individuals with lower endogenous hydrogen production.

Both HRW intervention groups exhibited significant improvements in key anthropometric and body composition measures, including reductions in body weight, BMI, waist circumference, and fat mass, as well as increases in fat-free mass, muscle mass, and total body water. These changes were consistent with prior studies demonstrating the metabolic benefits of molecular hydrogen intake, particularly with regard to adiposity reduction (Song et al., 2013; LeBaron et al., 2020). Notably, the effect size for change in waist circumference—a primary outcome—exceeded the conventional threshold for a large effect in both experimental groups, with a particularly pronounced effect observed in EXP1 (d = 1.77). This suggests that drinking HRW may be especially effective in reducing central adiposity, a key driver of cardiometabolic risk, particularly in individuals with lower baseline hydrogen levels. In contrast, the control groups exhibited minimal or no significant changes in most anthropometric parameters. However, modest improvements were observed in CON1 and CON2 for select indices, such as waist circumference and fat-free mass. These changes may reflect regression to the mean or non-specific effects related to behavioral monitoring, but they were markedly smaller than those observed in the HRW groups. The HRW intervention also produced significant improvements in a broad range of metabolic biomarkers. Both experimental groups showed significant reductions in fasting glucose, LDL and HDL cholesterol, triglycerides, APO-A and APO-B, and hs-CRP levels. These findings are consistent with previous reports highlighting the pro-metabolic and anti-inflammatory effects of molecular hydrogen in clinical populations (Nakao et al., 2010; Lugito et al., 2022; Chiu et al., 2023; Todorovic et al., 2023). Importantly, these biomarker improvements were observed irrespective of breath hydrogen stratification, indicating that HRW exerts robust metabolic benefits across varying levels of endogenous hydrogen production. Interestingly, no significant changes were observed for lipoprotein(a) and SOD activity, suggesting that these markers may be less responsive to HRW supplementation or require longer intervention periods for measurable effects. In contrast, the control groups generally maintained stable biomarker profiles, except for unfavorable increases in LDL cholesterol, APO-B, and hs-CRP (in CON1), and triglycerides (in CON2), reinforcing the specificity of the HRW effect. The significant time-by-treatment interaction effects for most anthropometric and biochemical outcomes underscore the differential impact of HRW relative to placebo. These interactions indicate that the magnitude of improvement over time depended on treatment allocation. Although no significant differences in effects were observed between the two experimental groups, the slightly larger effects in EXP1 (low breath hydrogen) support the hypothesis that individuals with lower endogenous hydrogen production may derive greater benefits from exogenous HRW intake. The potential for HRW to serve as a safe, non-pharmacologic adjunct to standard lifestyle interventions for metabolic syndrome is particularly promising given its high compliance rates, favorable safety profile, and minimal side effects. These findings align with the growing interest in personalized nutrition strategies, where interventions are tailored based on individual physiological traits—such as endogenous hydrogen production.

The precise biological mechanisms through which HRW exerts its beneficial effects in individuals with metabolic syndrome remain incompletely understood; however, several theoretical pathways have been proposed. Molecular hydrogen is traditionally recognized as a selective antioxidant, capable of scavenging hydroxyl radicals and peroxynitrite without interfering with essential redox signaling processes (Ohsawa et al., 2007; Trivic et al., 2017; Stajer et al. 2023). This redox-modulatory capacity may contribute to the observed reductions in systemic oxidative stress and inflammation, as evidenced by modulations in TAC, glutathione, and hs-CRP levels in the current study. However, the absence of significant effects of HRW on SOD activity observed in our study aligns with previous reports showing minimal or no influence of hydrogen on antioxidant capacity in other populations (Sim et al., 2020). These findings challenge the widely held notion of hydrogen as a universal antioxidant and instead suggest that its physiological benefits may be mediated through alternative mechanisms rather than direct free

radical scavenging alone. For instance, HRW may influence cellular metabolism by modulating key signaling pathways, including the AMP-activated protein kinase (AMPK) and nuclear factor erythroid 2–related factor 2 (Nrf2) pathways, both of which play crucial roles in glucose and lipid homeostasis, mitochondrial function, and oxidative stress response (Ichihara et al., 2015; Lin et al., 2015; Tsou et al., 2024). Emerging evidence also suggests that molecular hydrogen may affect gut microbiota composition and intestinal permeability, which in turn could indirectly influence host metabolic function (Korovljev et al., 2023b; Liang et al., 2023). Furthermore, hydrogen gas has been shown to induce mild hormetic stress responses that activate cytoprotective pathways, potentially enhancing cellular resilience to metabolic dysfunction (Dhilon et al., 2024). While these mechanistic hypotheses remain largely theoretical, the converging metabolic and anti-inflammatory benefits observed in the present trial underscore the need for future investigations incorporating molecular and cellular endpoints to elucidate the mechanistic underpinnings of HRW actions in humans with metabolic syndrome.

Several limitations of the present study should be acknowledged. First, the relatively short intervention duration of 12 weeks may not adequately capture the long-term efficacy, sustainability, or safety of HRW-induced changes in metabolic and physiological outcomes. Longitudinal studies with extended follow-up periods are warranted to determine the durability of observed benefits. Second, although the sample size was sufficient to detect moderate effect sizes for the primary outcome, the study's statistical power remains limited for detecting smaller effects or conducting subgroup analyses. Larger multicenter trials are needed to validate these findings in more diverse populations and to explore potential sex-, age-, or ethnicity-specific differences in response to HRW. Third, while participants were stratified based on baseline breath hydrogen concentrations, the threshold used to classify individuals into low and high endogenous hydrogen producers (10 ppm) was somewhat arbitrary and not based on universally accepted clinical cutoffs. Additionally, hydrogen metabolism is a dynamic and multifactorial process influenced by gut microbiota, dietary intake, and host metabolic function—factors not comprehensively assessed in this study. The decision to use a single baseline breath hydrogen measurement as the stratification criterion may not fully reflect an individual's typical hydrogen production capacity. Fourth, hydrogen levels were only measured in exhaled breath and not in other biological fluids such as blood, urine, or feces, which may have provided complementary insights into systemic hydrogen bioavailability and metabolism. Future research should incorporate a broader array of hydrogen biomarkers to more accurately characterize exposure and physiological distribution. Finally, dietary intake and physical activity levels were not tightly controlled during the intervention period, which could have introduced variability in metabolic outcomes and confounded the effects of the intervention. Although participants were instructed to maintain their habitual lifestyle practices, objective monitoring (e.g., dietary logs, accelerometers) was not implemented. Taken together, these limitations underscore the need for future mechanistic studies to clarify how molecular hydrogen modulates redox signaling, lipid metabolism, and inflammation in humans with metabolic stress. Moreover, investigating HRW in combination with established lifestyle interventions—such as dietary modification, structured physical activity programs, or pharmacological agents—may reveal additive or synergistic effects on metabolic health outcomes.

CONCLUSION

This randomized controlled trial provides novel evidence that HRW supplementation elicits clinically meaningful improvements in both anthropometric and biochemical markers of metabolic health among adults with metabolic syndrome. Over a 12-week intervention period, HRW significantly reduced central adiposity, improved body composition, and favorably modulated a range of metabolic biomarkers, including fasting glucose, lipid fractions, apolipoproteins, and inflammatory markers. These effects were observed across participants with varying levels of baseline endogenous hydrogen production, although individuals with lower breath hydrogen levels appeared to derive greater benefit, suggesting a compensatory advantage of exogenous hydrogen intake in this subgroup. Importantly, HRW was well tolerated, with high adherence and minimal adverse effects, further supporting its feasibility as a safe and non-pharmacologic adjunctive strategy for metabolic syndrome management. The findings underscore the therapeutic potential of HRW in mitigating cardiometabolic risk and contribute to a growing body of literature supporting molecular hydrogen as a bioactive compound with systemic metabolic effects. While the study's relatively short duration and modest sample size warrant cautious interpretation, the robustness of the observed effects and favorable safety profile highlight the need for larger, longer-term trials to confirm these findings and elucidate the mechanisms underlying metabolic actions of HRW. In particular, future research should explore the integration of HRW into personalized lifestyle intervention frameworks, particularly for individuals with impaired endogenous hydrogen production, to optimize its preventive and therapeutic utility in metabolic health.

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