Gastroenterology and Hepatology From Bed to Bench.
2024 **RIGLD**, Research Institute for Gastroenterology and Liver Diseases

SYSTEMATIC REVIEW

p-ISSN: 2008-2258 e-ISSN: 2008-4234

The impact of hydrogen-rich water on liver enzyme levels in clinical populations: a comprehensive review and meta-analysis

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ABSTRACT

Aim: This systematic review and meta-analysis aimed to assess the effect of hydrogen-rich water (HRW) on liver enzyme levels.
Background: Liver disease is a significant global health concern, greatly affecting mortality rates. Elevated levels of liver enzymes, such as ALT, AST, ALP, and GGT are early symptoms of liver disorders, and various approaches can help reduce them. Recent studies have shown the prospective therapeutic advantages of hydrogen as an antioxidant and anti-inflammatory agent in many circumstances.
Methods: The search strategy was developed following PRISMA guidelines. PubMed, Google Scholar, and Embase were searched from the beginning to January 2024. Eight Randomized controlled trial (RCT) studies were included, encompassing 433 participants with various liver function disorders.
Results: Our results showed a slight decrease in ALT, AST, and ALP levels in the treated group with HRW compared to the PW group.
Conclusion: Our findings suggest that consuming HRW may decrease liver enzyme levels in clinical populations. Further research is needed to confirm this relationship.

Keywords: Hydrogen-rich water, Liver enzymes, Hydrogen molecule, Meta-analysis.

(Please cite as: **Khalili-Tanha G, Jamialahmadi H, Rezaei-Tavirani M, Nazari E. The impact of hydrogen-rich water on liver enzyme levels in clinical populations: a comprehensive review and meta-analysis . Gastroenterol Hepatol Bed Bench 2024;17(4):338-348. https://doi.org/10.22037/ghfbb.v17i4.2990).**

Introduction

Liver disease is a major worldwide health issue, with a great effect on mortality rates. It causes two million deaths yearly, and accounts for 4% of all global deaths, which is equivalent to 1 out of every 25 deaths (1). Common risk factors for liver illnesses include excessive alcohol intake, obesity, diabetes, viral hepatitis infections (including hepatitis B and C), exposure to certain poisons or chemicals, and a familial predisposition to liver disease. Furthermore, certain medications and autoimmune conditions can increase the risk of developing liver diseases (2). Raising awareness about the risk factors and preventive measures associated with liver disease is crucial to reducing its prevalence and saving lives (1, 3). Early detection, lifestyle modifications, and access to proper medical care are essential in addressing this pressing public health issue. Early identification of hepatic disorders entails the surveillance of liver enzymes, which are proteins that catalyze biochemical processes in the liver. They are essential for metabolism, digestion, bile production, immunity, and detoxification (4, 5). Commonly measured liver enzymes in the blood tests include alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and gamma-glutamyl transferase (GGT) (6). Liver enzyme levels are frequently evaluated in clinical

Received: 18 May 2024 *Accepted*: 27 July 2024
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settings to assess liver function (7). Abnormal levels can indicate various liver diseases, including hepatitis, fatty liver disease, cirrhosis, or liver cancer (8, 9). Additionally, chronic liver disease frequently induces elevated insulin resistance, which is a critical characteristic of hepatogenous diabetes (10). The liver is the primary site of ALT and AST, and their concentrations in the blood are considered specific indicators of liver dysfunction (6). Elevated levels of GGT and ALP can indicate biliary tract disease, while elevated levels of ALP can indicate bone or intestinal disease (11). Elevated liver enzyme levels can result from certain medications, alcohol consumption, and other medical conditions (9).

In 2007, Ohsawa et al. found that hydrogen serves as a therapeutic antioxidant with the potential to protect cells and tissues from oxidative damage by reducing the peroxynitrite (ONOO–), and hydroxyl radical (·OH) (12). Furthermore, the researchers found that hydrogen can easily penetrate cell membranes and reach the mitochondria, where it exerts its antioxidant effects (12). Studies have demonstrated that hydrogen therapy has anti-inflammatory properties. It has been suggested that hydrogen can mitigate inflammation by decreasing the production of pro-inflammatory cytokines and oxidative stress (13). Hydrogen can reduce the side effects, enhance the effectiveness of traditional treatments, and improve the quality of life (14). There are different methods of hydrogen therapy, including inhaling hydrogen gas, injecting hydrogen-rich saline (HRS), HRW, and using hydrogen-infused creams (15).

Increasing the oxidative stress and inflammation are considered to be pathological mechanisms that lead to the onset and advancement of liver diseases like chronic viral hepatitis, and alcoholic liver diseases. Hydrogen therapy is a novel approach that can aid to reduce elevated liver enzymes, thereby lowering the risk of developing liver disease (16). Consequently, the objective of this meta-analysis was to compile and evaluate the data from prior research in order to ascertain the impact of HRW on liver enzyme levels in patients with liver disorders.

Methods

Literature search strategy and selection criteria

Relevant articles were performed via an electronic search of PubMed, Google Scholar, and Embase till January 2024, using following search keywords: ("molecular hydrogen" OR "Hydrogen-rich water" OR "HRW") AND ("liver diseases" OR "cirrhosis" OR "liver cancer" OR "fatty liver" OR "NAFLD" OR "NASH") AND ("liver enzyme" OR "alanine aminotransferase " OR "aspartate aminotransferase " OR "alkaline phosphatase"). The literature search was conducted by two individuals independently, and any uncertainties were resolved via the consultation with another author.

Inclusion and exclusion criteria

Articles included in this meta-analysis had to meet the following eligibility criteria: (1) The human experiments were published as an original article, (2) patients who experienced alteration of liver enzyme levels, including liver tumor, hepatitis, fatty liver, and insulin resistance, (3) studies comprising two groups HRW and pure water (PW), (4) randomized controlled trials, (5) have study indicators that included related liver enzyme alanine ALT, AST, and ALP.

Studies were excluded for following reasons: (1) non-English articles, (2) review articles, case reports, comments, guidelines, in-vivo, and in-vitro studies, (3) other types of hydrogen therapy, such as injection, inhalation, cream, and eye drops, (4) combination of HRW with other treatments, (5) the results lack a placebo group for comparison, (6) studies that lack pre- and post-treated data, (7) presented and published abstracts

Data extraction

The full text of each paper was screened in detail. Two researchers (H.J. and G.K.T) performed data extraction independently. Each research included the following information: first author's name and year of publication, study design, procedure, length, age, HRW and PW population, and results (with mean and standard deviation).

Quality evaluation of the included articles

Jadad scoring system was used to evaluate the quality of included articles. The assessment includes following 8 questions: (1) Was the study described as randomized? (2) Was the method of randomization appropriate? (3) Was the study described as blinding? (4) Was the method of blinding appropriate? (5) Was there a description of withdrawals and dropouts? (6) Was there a clear

description of the inclusion/exclusion criteria? (7) Was the method used to assess adverse effects described? (8) Were the methods of statistical analysis described (17)?

Statistical analysis

STATA 17.0 software package was utilized to conduct a meta-analysis using a random-effects modeling approach. The blood lipid profile's continuous variables were represented as mean and standard deviation (SD). Each meta-analysis used Cochrane Q test and I^2 index to evaluate study heterogeneity. If P>0.1 or $I^2 \leq 25\%$, it signified the absence of heterogeneity, leading to using a random effect model. Conversely, if P≤0.1 or $I^2>75\%$, it indicates substantial research heterogeneity, and the I^2 value between 25 to 50% is considered moderate. Forest plots visually assessed effect size and their corresponding 95% CIs across the studies. The distribution of funnel plot was employed to assess publication bias in the included literature, with P<0.05 indicating a significant difference.

Results

Literature search

The process of screening of studies is provided in PRISMA flowchart in Figure 1. In this research, we

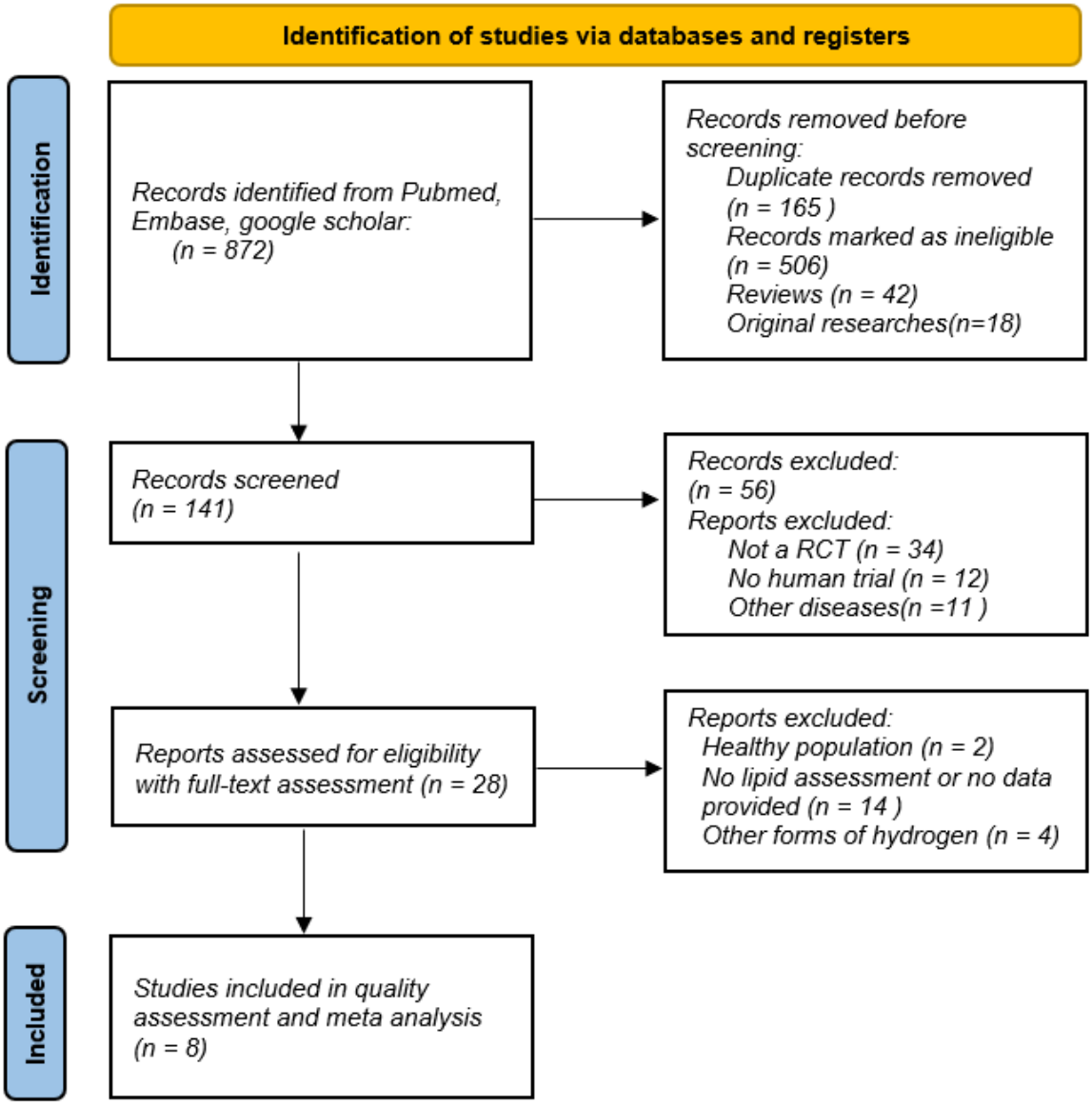

Figure 1. PRISMA flowchart of study selection

collected 872 types of literature and removed irrelevant studies, including 147 duplicate studies, 42 reviews, 18 originals, and 609 investigations, by reviewing titles and abstracts. Besides, full-text review of rest 56 studies, 28 studies were excluded because of the inconsistency of their studies. Finally, we included 8 studies for quality and meta-analysis assessment.

Study characteristics

The basic characteristics of 8 included Randomized controlled trial (RCT) studies are provided in Table 1. The research included 433 participants with various diseases impacting liver function. Data indicate that three trials included non-alcoholic fatty liver disease (NAFLD) (18-20), whereas individuals in two studies had type 2 diabetic mellitus (T2DM) or reduced glucose tolerance (21, 22). The patients of other studies had liver tumors (23) , and CRC with hepatic metastases (24), and in the last study, patients had chronic hepatitis B (25) .

All pertinent data on the studies meeting the inclusion criteria is displayed in Table 2. The overall

Table 1. Effects of hydrogen-rich- water on liver enzymes rate

Study	Population	Intervention	Outcomes
Kang et al. (2011)	25 patients with liver tumors (58.6±43.1 y)	**Study type:** Double-blinded, randomized, and placebo-controlled trials. **Protocol:** A combination of hydrogen-generating minerals provides around 0.55~0.65 mM of H2 daily with 500 mL water. **Period:** 6 weeks	There were no significant differences in AST and GGT levels between HRW and PW groups, while HRW decreased oxidative markers in liver tumor patients undergoing radiotherapy.
Xia et al. (2013)	30 patients with Chronic Hepatitis B (36.8±15.2 y)	**Study type:** Double-blinded, randomized, and placebo-controlled trials. **Protocol:** Oral HRW was administered thrice daily (1200–1800 mL/day). **Period:** 6 weeks	After HRW treatment, oxidative stress and liver function significantly improved, and HBV DNA decreased markedly after the respective treatments.
Yang et al. (2017)	76 patients with CRC with hepatic metastases	**Study type:** Double-blinded, randomized, and placebo-controlled trials. **Protocol:** A daily intake of 1,000 ml in four doses, 250 ml each, providing more than 0.27-0.4 ppm of H2. **Period:** 4 days	HRW exhibited no significant effect on liver function
Korovljeva et al. (2019)	12 patients with NAFLD (56.2±10 y)	**Study type:** Double-blinded, randomized, and placebo-controlled trials. **Protocol:** All patients receive 1 L daily HRW (3 mM hydrogen). **Period:** 28 days	HRW significantly attenuated serum levels of AST and liver fat deposition.
Ogawa et al. (2022)	23 patients with T2DM (66±8 y)	**Study type:** Double-blinded, randomized, and placebo-controlled trials. **Protocol:** H2 is administered via EHW. Participants were instructed to consume 1,500–2000 mL of water daily, and the electrolyte levels gradually increased over time. **Period:** 3 months	The ALT and urinary uric acid excretion volume were significantly lower in the EHW group compared to the FW group.
Kura et al. (2022)	17 patients with NAFLD (52.65±11.9 y)	**Study type:** Double-blinded, randomized, and placebo-controlled trials. **Protocol:** one tablet thrice daily with 330 mL of water (providing more than 4 mg of H2 daily). **Period:** 8 weeks	There was no significant difference in liver enzymes between HRW and PW groups, while BMI and systolic blood pressure reduced dramatically.
Liang et al. (2023)	32 patients with IFG (46.16±6.02 y)	**Study type:** Double-blinded, randomized, and placebo-controlled trials. **Protocol:** one L/d of HRW (H2 concentration = 1.4 mg/ml), **Period:** 8 weeks	HRW showed a substantial decrease in fasting blood glucose and total cholesterol (TC) levels in patients with IFG. Also, H2 improved metabolic abnormalities and dysbiosis of gut microbiota.
Sumbalová et al. (2023)	17 patients with NAFLD (52.6±2.9 y)	**Study type:** Double-blinded, randomized, and placebo-controlled trials. **Protocol:** one tablet daily with 330 mL of water (providing more than 4 mg/L of H2 daily). **Period:** 8 weeks	No significant difference in the levels of ALT, AST, and GMT was observed in the HRW group.

Abbreviations: Alanine transaminase (ALT), Aspartate transaminase (AST); Gammaglutamyl transferase (GMT); Electrolyzed hydrogen-rich water (EHW); Filtered water (FW); Type 2 diabetes (T2DM), Impaired fasting glucose (IFG), Non-alcoholic fatty liver disease (NAFLD), Colorectal cancer (CRC)

periods of these studies ranged from 4 days (24) to 3 months (21). The administrated volumes of HRW for the participants of these studies for treated groups ranged from 500 ml to 2000 ml per day, however, half of the studies used approximately 1000 ml/day (18-20, 22, 24). Although most of the studies provided the concentrations of administrated HRW (19, 20, 22-24), we did not find these data in others.

Considering the context of liver enzyme alterations including AST, ALT, and ALP, four research analyzed all of these enzymes (19, 20, 22, 24), while two studies solely evaluated the ALT in their investigations (21, 25). Korovljeva et al. just studied the changes in AST (18), and Kang et al. assessed the AST and ALT enzymes on their RCT (23).

Quality assessment

Jadad quality assessment was used to evaluate the quality of the included studies. Based on the scoring and methodology of these studies, as shown in Table 3,

Table 2. Basic information and the liver enzyme rates of the included studies

Author, year	Research object	Total cases		AST (μkat/l)		ALT (μkat/l)		ALP (μkat/l)	
		HRW	PW	HRW	PW	HRW	PW	HRW	PW
Kang et al. (2011)	Liver tumors	25	24	0.44±0.13	0.43±0.11	0.46±0.1	0.48±0.23		
Xia et al (2013)	Chronic Hepatitis B	30	30			0.91±0.57	1.13±0.64		
Yang et al. (2017)	CRC with hepatic metastases	76	60	0.39±0.04	0.65±0.08	0.52±0.02	0.97±0.04	1.12±0.055	1.17±0.08
Korovljeva et al. (2019)	NAFLD	12	12	0.056±0.22	0.33±0.101				
Ogawa et al (2022)	Insulin resistance	23	20			0.3±0.07	0.39±0.2		
Kura et al. (2022)	NAFLD	17	13	0.53±0.22	0.48±0.14	0.75±0.3	0.58±0.24	1.32±0.55	1.09±0.37
Liang et al. (2023)	IFG	32	41	0.31±0.12	0.35±0.1	0.33±0.32	0.38±0.33	1.09±0.287	1.22±0.3
Sumbalová et al. (2023)	NAFLD	17	13	0.55±0.05	0.41±0.04	0.75±0.07	0.45±0.07	1.34±0.13	1.26±0.1

Abbreviations: Alanine transaminase (ALT), Aspartate transaminase (AST); Gammaglutamyl transferase (GMT); Electrolyzed hydrogen-rich water (EHW); Filtered water (FW); Type 2 diabetes (T2DM), Impaired fasting glucose (IFG), Non-alcoholic fatty liver disease (NAFLD), Colorectal cancer (CRC)

Table 3. Jadad quality control scoring of the included studies

Questions (YES=1 NO=0)	Kang et al. 2011)	Xia et al (2013)	Yang et al. (2017)	Korovljeva et al. (2019)	Ogawa et al (2022)	Kura et al. (2022)	Liang et al. (2023)	Sumbalová et al. (2023)
Was the study described as randomized?	1	1	1	1	1	1	1	1
Was the method of randomization appropriate?	0	0	0	0	1	1	0	1
Was the study described as blinding?	0	1	1	1	1	1	1	1
Was the method of blinding appropriate?	0	0	0	0	1	0	0	0
Was there a description of withdrawals and dropouts?	0	1	1	0	1	1	1	0
Was there a clear description of the inclusion/exclusion criteria?	1	1	1	1	1	1	1	1
Was the method used to assess adverse effects described?	0	0	0	0	1	1	0	0
Were the methods of statistical analysis described?	1	1	1	1	1	1	1	1
Total Score	3	5	5	4	8	7	5	5

seven studies' qualities evaluated “good” to “excellent” and scored between 4 to 8, and just one study scored 3 and was considered “moderate” (23) .

For the evaluation of publication bias risk of these studies, we used Hedges’s method as shown in the funnel plots in Figure 2.

Evaluation of the liver enzyme rates after treatment with HRW

ALT

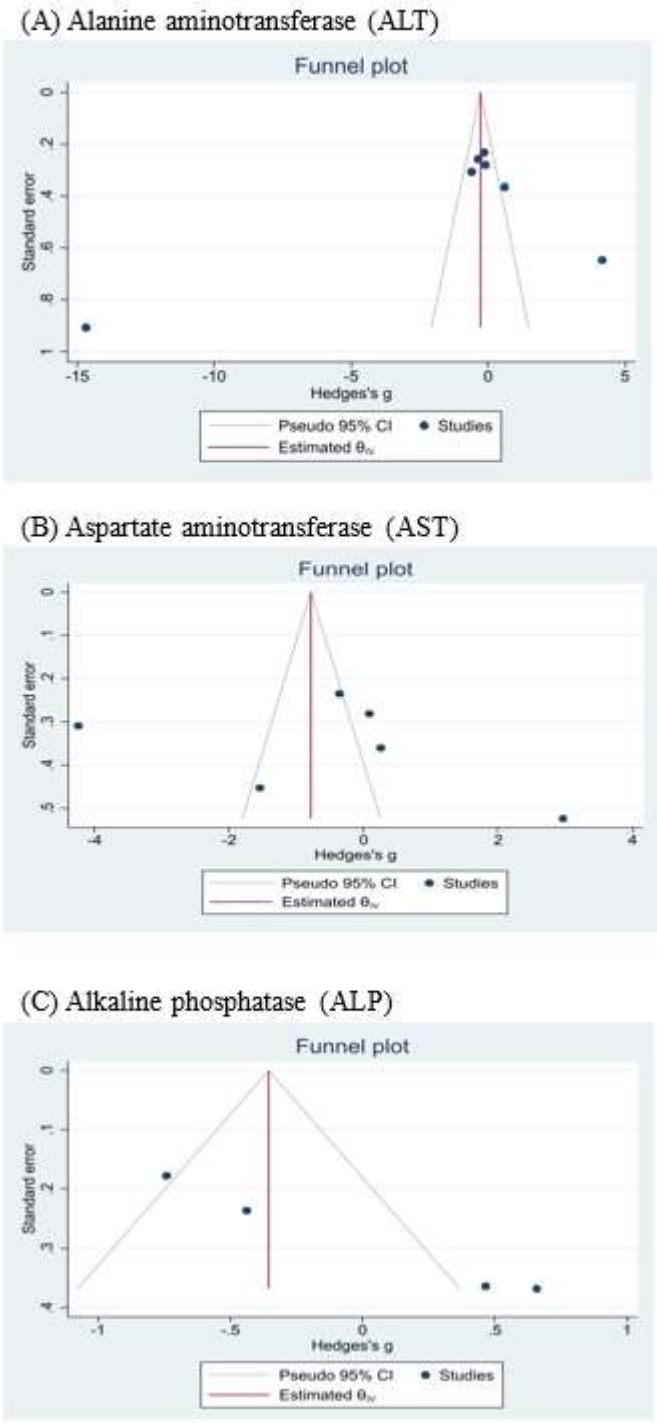

Figure 2. Publication bias assessment with Hedges’s method; Funnel plots of the included studies show no publication bias in the association between HRW and liver enzymes.

The liver ALT level changes in various pathogenic conditions. The assessment of pooled ALT changes after treatment with HRW is shown in Figure 3 Based on these data, ALT decreased after HRW therapy in patients, compared with the PW-treated group (95% CI: -1.56 (-5.95, 2.82)). Therefore, the heterogeneity assessment showed heterogeneity with I^2= 99.68%.

AST

To determine AST changes in liver-related disease after treatment with HRW, we assessed the results of 8 filtered studies. AST somewhat decreased after HRW treatment in comparison to the control group, but the changes were not statistically significant, based on the aggregate 95% CI of these investigations (Figure 3).

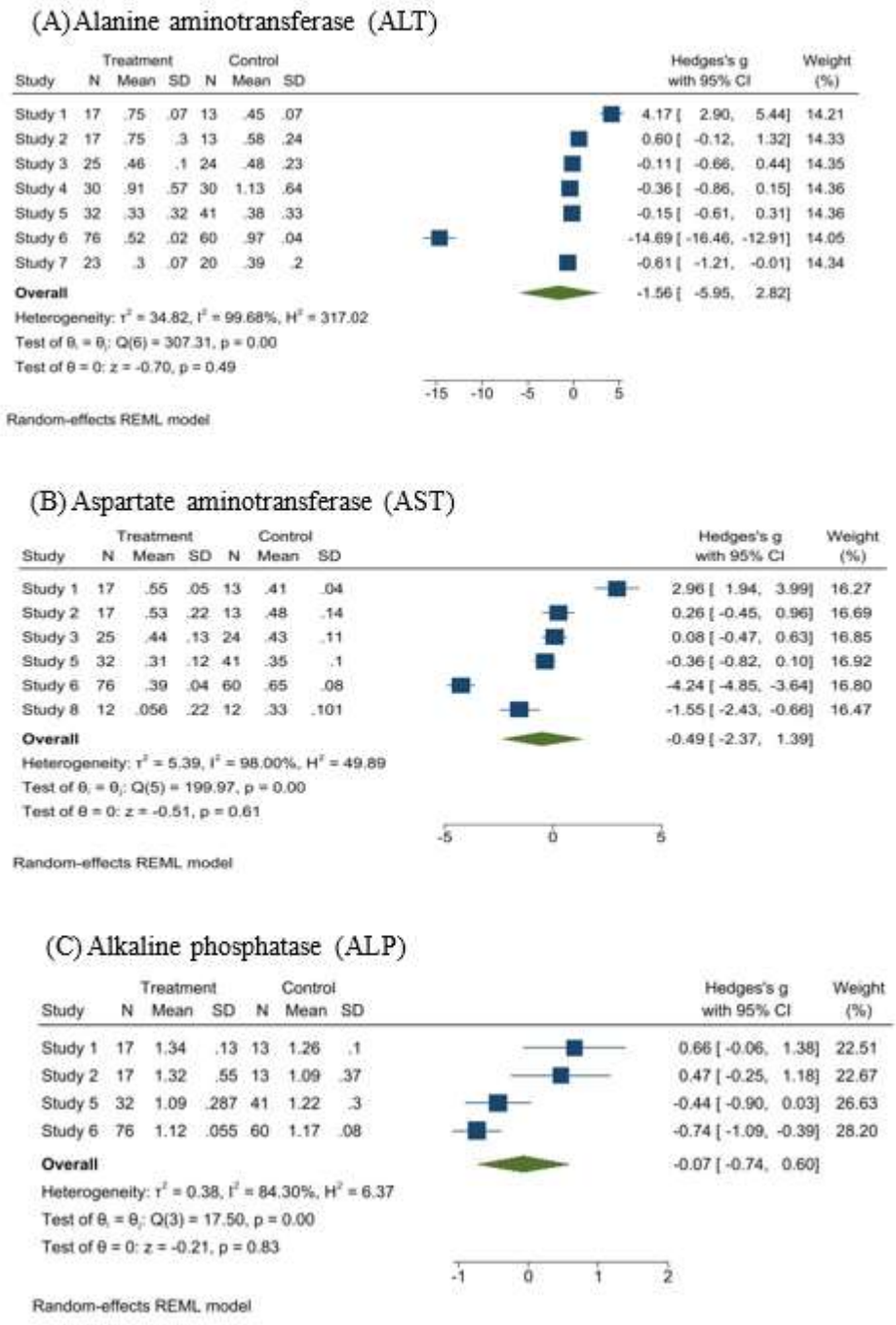

Figure 3. Forest plot illustrating the impact of HRW supplementation on liver enzyme levels and the variations in liver ALT levels across different pathogenic conditions.

Additionally, as seen in Figure 2 (I^2 = 98%), heterogeneity was noted in these studies.

ALP

ALP enzyme changes after treatment with HRW in different liver dysfunctions were evaluated based on random effect heterogeneity in all 8 studies. We found that the ALP changed very slightly after treatment with HRW compared to the groups that received PW ((%95 CI=-0.07 (-0.74, 0.60)). Furthermore, as shown in Figure 3, we evaluated the heterogeneity bias of studies and found a considerable heterogeneity according to the I^2 value(I^2=84.3%).

Discussion

This systematic review and meta-analysis aggregated and synthesized contemporary scientific literature to assess the possible effects of HRW intake on liver enzyme levels in clinical populations. Eight RCT studies were included, encompassing 433 participants with various liver function disorders. Our results showed a slight decrease in ALT, AST, and ALP levels in the treated group with HRW compared to PW group.

The HRW role in NAFLD

Three studies examined the effect of HRW on NAFLD (26-27). NAFLD is a major cause of liver disease globally, with an increasing incidence rate, and an estimated global prevalence of 25% (28). This condition involves the accumulation of excess fat in the liver, leading to inflammation and damage. Liver enzymes like ALT and AST are frequently elevated in individuals with NAFLD, serving as markers of liver inflammation and damage(29). A cohort research including 129 individuals with NAFLD revealed that increased liver enzyme levels are significantly correlated with advanced liver disease stages and reduced overall survival (OS). Furthermore, they showed that NAFLD patients with high levels of liver enzymes experience impaired glucose tolerance (IGT), and T2DM (30). Another study revealed that the serum levels of ALP and GGT improved, while the level of albumin decreased in 73 patients with NAFLD (31). Huang et al. showed that the patients with NAFLD, and elevated liver enzyme levels have a higher risk of developing cirrhosis, and hepatocellular Carcinoma (HCC), and therefore should be closely monitored (32). Korovljev et al. examined the therapeutic effect of hydrogen in a group of 12 overweight patients with NAFLD. They found that HRW notably enhanced the serum liver enzyme profile by lowering AST levels and liver fat accumulation (26). Kura et al. found no significant difference in liver enzymes between HRW and PW groups. Nonetheless, both BMI and systolic blood pressure exhibited a considerable reduction. Their study included 17 NAFLD patients (mean age 52.65±11.9 years) who ingested one tablet thrice daily with 330 mL of water (delivering over 4 mg of H2 daily) for a duration of 8 weeks (20). In a 2023 study by Sumbalová et al. on 17 NAFLD patients with elevated liver enzymes, no significant differences in ALT, AST, and GMT levels were noted in the HRW group (27). Researchers studied the effect of molecular hydrogen on 43 NAFLD patients, an animal model, and in an in-vitro study. They found that hydrogen/oxygen inhalation inhibited liver fat accumulation and enhanced lipid and liver enzymes in NAFLD patients. The animal study showed a significant improvement in blood lipid levels, inflammation, and liver histology in NASH-induced mice (33).

The HRW role in cancer

Two studies evaluated the effect of HRW on cancer. A large body of evidence reported that elevated levels of liver enzymes as a prognostic marker in HCC which are associated with aggressiveness (34). Xu et al. showed that tumor-free survival (TFS) and OS were worse in HCC patients with higher levels of GGT and ALP, indicating their role in diagnosis and prognosis (35). Kang et al. revealed that regular drinking of hydrogen-rich water might be a potential treatment technique to improve the quality of life for liver cancer patients receiving radiation. Patients who consumed hydrogen-rich water showed no significant differences in AST and GGT levels between HRW and PW groups. However, HRW reduced oxidative markers in liver tumor patients undergoing radiotherapy (36). An investigation of CRC patients with liver metastases who received the mFOLFOX6 regimen showed a significant increase in liver enzymes. The study assessed the effect of hydrogen-rich water on the levels of AST and ALT but found no significant effect (37). The research of advanced non-small cell lung cancer patients found that the control group (patients who

denied therapy) had a worse progression-free survival rate than the group treated exclusively with H2. Furthermore, their survival was notably lower than the combination groups of H2 with chemotherapy, H2 with targeted therapy, and H2 with immunotherapy (48). Another study indicated that the patients with advanced non-small cell lung cancer who underwent 2 weeks of hydrogen inhalation showed a significant reversal of senescence in adaptive and innate immune systems. All six immune cell subsets increased to within the normal range (49).

The HRW role in chronic hepatitis B

Chronic hepatitis B is a long-term infection of the liver caused by the hepatitis B virus. It can lead to liver damage, cirrhosis, and even liver cancer if left untreated. Chronic hepatitis B patients often have increased liver enzymes (40). ALT, AST, and GGT levels increased in a cohort study of 10,741 hepatitis B patients, increasing the chance of developing diabetes mellitus (41). In current meta-analysis, one study evaluated the effect of HRW on patients with chronic hepatitis B and their results showed that liver function and oxidative stress were improved and HBV DNA decreased markedly after the respective treatments (42).

The HRW role in diabetes

Impaired Fasting Glucose (IFG), also known as pre-diabetes is a condition where blood glucose levels are higher than normal but not high enough to be considered diabetes. Type 2 diabetes mellitus (T2DM) is a chronic condition where the body becomes resistant to insulin or doesn't produce enough insulin to maintain normal blood glucose levels (43). The likelihood of developing type 2 diabetes in the future is elevated by the presence of IFG. An increase in liver lipid accumulation, inflammation, and oxidative stress can result in elevated levels of liver enzymes as a consequence of diabetes and insulin resistance (44). A study reported that the level of liver enzymes is a potential biomarker to predict the increased glucose levels in diabetic patients. Gender differences play a critical role in the function of each liver enzyme regarding high blood glucose levels. GGT proved to be a better indicator for elevated blood glucose in males, while ALT and ALP were more effective for females (45). Ko et al. showed that the elevated level of GGT and ALT and reduced level of AST/ALT are linked to an increased risk of type 2 diabetes. The combination of two markers was evaluated. The results showed that the combination of AST/ALT and GGT, and the combination of AST/ALT and ALT increased the risk of T2DM in women and men, respectively (46). In the current meta-analysis, two studies evaluated the effect of hydrogen-rich water on T2DM and IFG (47, 48). Twenty-three T2DM patients were treated with electrolyzed hydrogen-rich water (EHW) to see how hydrogen affected oxidative stress. Liver enzyme levels were also assessed, and EHW group had considerably lower ALT and urine uric acid excretion volume than the control group (48). Liang et al. found that while there was no difference in the ALP level in the HRW group, there was a significant decrease in fasting blood glucose and total cholesterol (TC) levels in the patients with IFG in the HRW group. Therefore, H2 improved metabolic abnormalities and dysbiosis of gut microbiota (47).

This meta-analysis has several limitations. First, significant heterogeneity exists among the included studies, which differ considerably in design, sample sizes, and overall quantity. This variability can affect the reliability and consistency of the results. To mitigate this, subgroup analyses based on study design and sample size were conducted, along with random-effects models to account for variability. Second, patients in the studies come from a variety of demographic and cultural backgrounds, and their treatment plans vary. The interpretation of the results may be made more difficult by this variety. Stratified analyses were used to assess the influence of various demographic and ethnic backgrounds on treatment outcomes, providing a more comprehensive understanding of the results.

Conclusion

This represents the initial exhaustive systematic review and meta-analysis of the literature regarding the correlation between liver enzyme levels, such as ALT, AST, ALP, and GGT, and the impact of hydrogen-rich water in clinical populations. Recent prospective studies indicate a slight decrease in liver enzymes among the population. Future studies should investigate the potential antioxidant, and anti-inflammatory mechanisms behind the effects of hydrogen-rich water on liver enzyme levels.

Conflict of interests

There is no conflict of interest for authors of this article.

Funding

This study was supported by a grant from the Shahid Beheshti University of Medical Science to Elham Nazari.

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