

Effect of hydrogen-rich water on periodontal disease, interleukin and blood glucose levels in diabetic

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ABSTRACT Diabetes Mellitus (DM) is a metabolic disorder characterized by high blood glucose levels associated with periodontal disease and increased levels of inflammatory biomarkers such as interleukin. Therapeutic effects of molecular hydrogen for a wide range of disease models and human diseases have been investigated. This review aims to systematically analyze and review animal and human studies investigating the effect of HRW on periodontal tissues, interleukin, or blood glucose levels. An electronic search was conducted via PubMed/Medline, Google Scholar, Wiley Online Library, LILACS, Science.gov, and Cochrane Central Register of Controlled Trials (CONTROL) using the keywords "Hydrogen Water", "Diabetes Mellitus", "Interleukin" and "Periodontal disease" for studies published between January 2011 to May 2021. After the elimination of duplicate items, the primary search resulted in 101 articles. After excluding irrelevant articles based on abstract and title, full texts of 45 articles were read to exclude additional unrelated studies. Eight studies were included in this review for qualitative analysis. The results showed that Drinking HRW exerts certain antioxidants for oxidative gingival stress and anti-inflammatory effects by decreasing interleukin and decreasing blood glucose levels for DM patients.

KEYWORDS: HRW, DM, Periodontal disease, interleukin

INTRODUCTION

Diabetes Mellitus is a metabolic disorder characterized by high blood glucose levels. High amounts of plasma glucose may cause damage to the blood vessels, nerves, and body organs.¹ There are two main types of DM. Type 1 Diabetes Mellitus (T1DM) occurs due to insulin deficiency caused by immune-mediated destruction of the pancreas' beta cells, which produce insulin. In type 2 Diabetes Mellitus (T2DM), insulin is resistant to its receptor in muscle, fat, and other cells and causes activation of the compensatory mechanism inducing β -cells to secrete more insulin.² T2DM occurs when the compensatory increase in insulin is insufficient to maintain blood glucose levels within the normal physiological range. Uncontrolled Diabetes Mellitus may lead to many complications, including delayed

wound healing, stroke, renal failure, anxiety, retinopathy, and limb amputation.^{1,3}

The number of people with diabetes is projected to increase from 171 million in 2000 to 366 million in 2030. Its prevalence has increased more rapidly in middle and low-income countries, so it deserves attention in dentistry. Metabolic disorders increase inflammation of the periodontal tissues, alter bone turnover, and increase the risk of alveolar bone loss.² Due to a compromised immune system and reduced salivary flow, individuals with DM have a higher incidence of dental caries, periodontal disease, and oral infections. Similarly, as observed in clinical studies, DM decreased osteoblast function and consequently reduced bone density. Clinical studies have shown that diabetes increased pro-

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inflammatory factors that accelerate bone resorption, leading to reduced bone mineral density.^{2,4}

Most patients with DM show gingival inflammation and a high risk for periodontitis. Periodontitis is a chronic disease of the tooth-supporting tissue, characterized by gingival bleeding, periodontal pocket formation, connective tissue damage, and alveolar bone loss.^{4,5} The subgingival plaque biofilm is responsible for the onset and progression of periodontitis. An abnormal immune response to pathogenic bacteria is also accepted as a risk factor for the development of periodontitis.⁶ Patients with DM have been systematically observed to experience an increase in prevalence and intensity of periodontal disease compared with healthy patients.⁷ A prolonged increase in blood glucose levels leads to advanced glycosylated end products (AGEs). Periodontitis occurs when AGEs react with receptors of advanced glycosylation end products (RAGE) in the periodontal tissue. In addition, studies have shown that DM inhibits bone remodeling around teeth undergoing orthodontic tooth movement.^{3,7,8}

Periodontitis is caused by pathogenic microorganisms that activate an immunoinflammatory response of the host.^{8,9,10} Mediators released by inflammatory cells stimulate periodontal cells to secrete metalloproteinases, proteolytic enzymes that are directly responsible for connective tissue destruction, and prostaglandins, contributing to the destruction of the alveolar bone. Gene polymorphisms encoding Interleukin (IL)-1 are the most prominent gene polymorphisms in studies on periodontitis. IL-1 is a family of at least ten molecules. The two most significant ones in the pathogenesis of periodontitis are IL-1 α , connected with the cell, and IL-1 β , released into the environment and showing agonistic action upon binding with a receptor.^{11,12}

IL-1 β is a regulator of the body's inflammatory response and is produced after infection, injury, and antigenic challenges. It plays a role in various diseases, including autoimmune diseases such as rheumatoid arthritis, inflammatory bowel disease, type 1 diabetes, diseases associated

with metabolic syndromes such as atherosclerosis, chronic heart failure, and type 2 diabetes.¹³

IL-1 β was found to induce β -cells death, which is enhanced by the cytokines IFN γ and TNF α . IL-1 β has been shown to interfere with insulin release, induce Fas expression, and thus allow Fas-induced apoptosis in rodent and human islets, and share similarities with glucose-induced apoptosis. In line with the critical role of glucose in mediating insulin secretion and proliferation, low IL-1 β concentrations also stimulate insulin release and proliferation in rat and human islets.^{12,14}

Reactive oxygen species (ROS) are products of normal immune responses against bacterial pathogens. Still, excess production of ROS causes oxidative stress, and such conditions damage DNA, proteins, and lipids in host tissues. There is a close relationship between oxidative stress and chronic inflammation.^{15,16,17}

Molecular hydrogen has been identified as one of the antioxidants that can reduce oxidative stress.¹⁸⁻²² Drinking water that contains a therapeutic hydrogen dose of hydrogen-rich water (HRW) is an easy method of sending molecular hydrogen into the body. Several studies on HRW show that it can reduce blood sugar levels in DM patients. Kajiyama (2008) states that hydrogen water can prevent or delay the development of T2DM and insulin resistance by protecting against oxidative stress.²¹

Kasuyama (2011) reported that the antioxidant effect of HRW could suppress periodontitis, but its effect on bacteria that cause periodontal disease has not been confirmed.²² In previous studies, it also showed that taking HRW can stop ligature-induced periodontitis in mice. Azuma (2015) also showed that drinking HRW has additive effects on the non-surgical periodontal treatment of improving periodontitis.²³ Kim (2017) said HRW could inhibit the biofilm of pathogenic bacteria. However, no systematic review has been published to summarize and critically analyze the studies undertaken on this topic.²⁴ Therefore, this review aims to summarize the literature on the effect of HRW on periodontal disease, interleukin, or blood glucose levels in diabetic and non-diabetic patients.

MATERIALS AND METHODS

Focused question

The following research questions were developed using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement: "What is the effect of HRW on periodontal disease?" "What is the effect of HRW on

interleukin?" and "What is the effect of HRW on blood glucose level in diabetic subjects?"

Selection criteria

The following types of studies were included in this review: (1) prospective clinical trials,

(2) animal and human models, (3) assessment of HRW effects in diabetic subjects, (4) effect of HRW on Interleukin or periodontal diseases, (5) English language, and (6) HRW by drinking. Reviews, case reports and series, commentaries, letters to the editor, short communications, and administration of hydrogen water besides drinking (saline, spray, subcutaneous, or injection) were excluded.

Search methodology

An electronic search was conducted in PubMed/Medline databases, using the Medical Subject Headings (MeSH) terms "Hydrogen Water", "Diabetes Mellitus", "Interleukin", "Periodontal disease" and combination between them, such as

"hydrogen water or periodontal disease", "hydrogen water and diabetes", or "hydrogen water and Interleukin" and the studies published between January 2011 to May 2021. A similar search was conducted via Google Scholar, Wiley Online Library, LILACS, Science.gov, and Cochrane Central Register of Controlled Trials (CONTROL). A secondary search was conducted by reading the reference lists of the articles meeting the inclusion criteria for additional studies relevant to this review. A summary of the search criteria and MeSH terms used for searching via PubMed is presented in Table 1.

Table 1. A summary of MeSH terms, inclusion criteria, and exclusion criteria used for extracting literature from PubMed for this study

MeSH terms	Inclusion criteria	Exclusion criteria
"Hydrogen Water", "Diabetes", "Interleukin" and "Periodontal disease"	(1) Prospective clinical trials (2) Animal studies (3) Studies assessing the effect of HRW in diabetic subjects (4) Effect of HRW in Interleukin or periodontal disease, (5) Studies in English (6) HRW administration by oral intake (drinking)	Reviews Case reports and series Commentaries Letters to the editor Short communications Hydrogen administration by saline, spray, or subcutaneous

RESULTS

After eliminating the duplicate items, the primary search produced 101 articles. After exclusion of irrelevant articles based on abstract and title, full texts of 45 articles were read to exclude additional unrelated studies. Eight studies were included in this review for qualitative analysis. The PRISMA flow chart (**Fig. 1**) illustrates the search methodology and results.²⁵

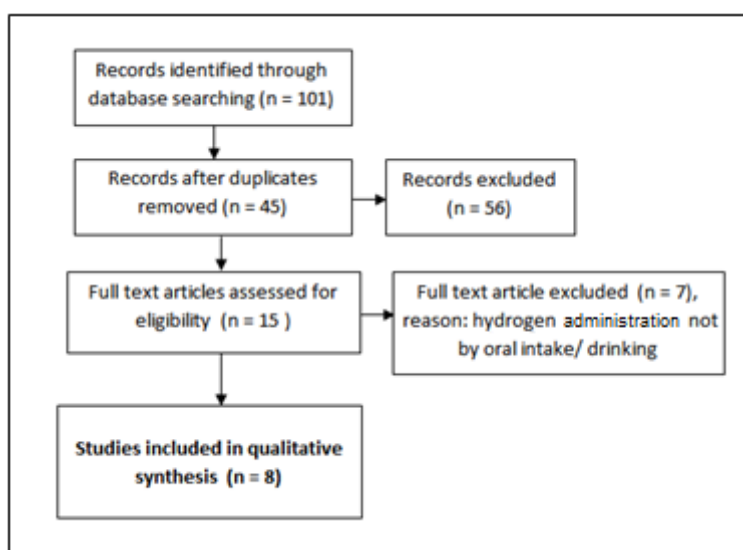


Figure 1. PRISMA flow diagram for the search process employed for this review

Table.2

General characteristics and outcome of studies conducted on the effect of HRW on periodontal tissues, interleukin, and Blood glucose level

NO	Author, year	Sample	Study Groups	Duration	HRW Concentration	Target	Outcomes	Ref
1	Azuma et al, 2015	Thirteen patients (3 women, 10 men) with periodontitis	Two groups: 1. The control group ($n = 6$) 2. The HW group ($n = 7$)	8 weeks	HRW group drank 200–300 mL of HW every time, 4–5 times/day for a total of 1000 mL (no concentration explanation)	Periodontal	HRW group showed greater improvements in probing pocket depth and clinical attachment level than the control group. HRW group also exhibited an increased serum level of total antioxidant capacity at four weeks	23
2	Kasuyama et al, 2011	Twenty-eight male Wistar rats (8weeks-old)	four groups of seven rats each: (i) Control group (ii) HRW group (iii) Periodontitis group (iv) Periodontitis + HRW group	4 weeks	hydrogen concentration; 800–1000 $\mu\text{g/l}$	Periodontal tissues	Consuming hydrogen-rich water might be beneficial in suppressing periodontitis progression by decreasing gingival oxidative stress.	22
3	Tomofuji et al, 2014	Four-month-old male Fischer 344 rats ($n=18$)	Two groups: 1. HRW group ($n=6$) 2. The control group ($n=6$, distilled water treatment).	12 months	hydrogen concentration was ≥ 500 mg/L (1 hour after electrolysis of water)	Periodontal tissues, IL	Drinking hydrogen-rich water is proposed to have anti-aging effects on periodontal oxidative damage. Gene expression of NLRP3, caspase-1, and IL-1b in periodontal tissues obtained from the experimental group was	26

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							significantly higher in the experimental group than in the control group.	
4	Yoneda et al, 2017	Male Fischer 344 rats (n = 18)	three groups of six rats each: 1. Control group (normal Diet) 2. High Fat Diet Group (HFD) 3. HFD + HRW	12 weeks	Concentration after 1 min was $301.7 \pm 65.1 \mu\text{g/L}$, and that after 24 h was $186.3 \pm 55 \mu\text{g/L}$.	Periodontal tissues, DM	Drinking HRW can inhibit gingival oxidative stress induced by obesity, and thus prevent alveolar bone resorption in rat models.	19
5	Zheng et al, 2021	Wistar rat	3 groups 1. control (normal rats, n=10) 2. DM rats (HFD+STZ, n=15) 3. DM rats +HRW (HFD+STZ + HRW, n=15)	3 weeks	Above 1.0 ppm	DM	The results showed that drinking HW suppressed the increase in glucose, total cholesterol, oxidative stress, and inflammation. Moreover, HW also ameliorates hyperglycemia-induced liver, kidney, and spleen dysfunction.	27
6	Lebaron et al, 2020	60 subjects (30 men and 30 women) with metabolic syndrome, prediabetes/ diabetes (fasting glucose > 110 mg/dL)	2 groups Placebo & HRW	24 weeks	>5.5 millimoles H ₂ /day	DM, IL	Supplementation with high-concentration HRW significantly reduced blood cholesterol and glucose levels, attenuated serum hemoglobin A1c, and improved biomarkers of inflammation and redox homeostasis. Furthermore, HRW significantly attenuated the inflammatory markers, such as TNF- α , IL-6, and CRP.	28

7	Sha et al, 2018	Thirty-eight juvenile female football players from the Suzhou Sports School	two groups: the control group (n = 10) and HRW treatment group (n = 28)	8 weeks	drinking	IL	Long-term consumption of hydrogen-rich water not only exerts certain antioxidant and anti-inflammatory effects but also enhances the diversity and abundance of the gut flora of the subjects. Levels of serum MDA, IL-1, IL-6, and TNF- α decreased in the HRW groups.	29
8	Kajisa et al, 2017	male 12-week-old NC/Nga mice	HRW-treated (n=11) and PW-treated (n=9) groups	4 weeks	1.0 $\pm$ 0.1 ppm	IL	Hydrogen water downregulated IL-1 β and IL-33 secretion in AD skin lesions and prevention of mast cell infiltration at the lesion site.	30

The eight quantitative studies selected for this review published between 2011 and 2021 were analyzed by reading the abstract, objective, analytical data to gather information about the effect of hydrogen water on periodontal disease, interleukin, or blood glucose levels in patients or without diabetes. In these studies, four studies were

conducted on animals and four others on human models. HRW was consumed in varying concentrations via drinking. Four studies examined the effect of HRW on periodontal disease, while three studies examined the impact of HRW on diabetes mellitus. Table 2 summarizes the studies' general characteristics.

DISCUSSION

DM has many implications on human health, especially uncontrolled DM, it may damage various organs and tissues. Moreover, uncontrolled DM may also lead to delayed wound healing, recurrent oral ulceration, affects bone metabolism, and leads to osteoporosis; however, its pathogenetic mechanisms remain unknown. High glucose conditions induced the production of reactive oxygen species (ROS) and associated with periodontal disease and increased levels of inflammatory biomarkers such as interleukin-1 β (IL-1 β), tumor necrosis factor- α (TNF- α), interleukin-6 (IL-6), and c-reactive protein (CRP).^{7,12,13}

Interleukins (ILs) are a group of cytokines that were first seen to be expressed by white blood cells (leukocytes). They play an essential role in the activation and differentiation, proliferation,

maturation, migration, and adhesion of immune cells. They also have pro-inflammatory and anti-inflammatory properties.^{11,12} Therefore, the primary function of interleukins is to modulate growth, differentiation, and activation during inflammatory and immune responses. Interleukins consist of a large group of proteins that can induce many reactions in cells and tissues by binding to high-affinity receptors on the cell's surface.¹²

It has also been reported that the islets of the pancreas produce and secrete IL-1 β . Insulin-producing β -cells in the islets of the pancreas is particularly susceptible to IL- β -induced damage and loss of function. The production of IL-1 β -derived macrophages in insulin-sensitive organs leads to inflammation and induction of insulin resistance in obesity. Liu (2020) and Maedler (2011) reported the mechanisms involved in

inflammation and, in particular, the IL-1 β signaling lead to the development of insulin resistance and diabetes.^{12,13}

Diseases associated with metabolic syndrome are characterized by abnormal cytokine production, including increased circulating IL-1 β , elevated acute-phase proteins, e.g., CRP, and inflammatory signaling pathways. Pro-inflammatory cytokines can cause insulin resistance in adipose tissue, skeletal muscle, and liver by inhibiting insulin signal transduction. The source of cytokines in an insulin-resistant state is the insulin-target tissue itself, obese and liver, but most of these are activated tissue-dwelling macrophages. While the infiltration of macrophages in adipose tissue and the brain has been shown in many studies, increased islet macrophage infiltration has recently been observed in the pancreas of patients with T2DM. In T2DM animal models, such as GK, HFD, and db/db mice,¹² At the same time, IL-1 β signaling causes damage and impaired insulin secretion in β -cells, insulin signaling is impaired in the insulin-target tissue. Maintaining the mass and function of β -cells to achieve normal glycemia is the main goal of diabetes therapy.^{13,14}

In dentistry, clinical studies have revealed that periodontitis is correlated with increased oxidation of lipids, DNA, and proteins in gingival crevicular fluid, saliva, or blood. Oxidative stress is involved in periodontitis's pathogenesis, and reducing oxidative stress by consuming antioxidants will be potentially therapeutic in periodontitis.¹⁵ In the periodontal tissue, host cells such as polymorphonuclear leucocytes produce reactive oxygen species (ROS) as part of the host defense against bacterial pathogens.^{11,13} ROS can disturb the oxidant-antioxidant balance, leading to many inflammatory diseases, such as diabetic osteoporosis.^{20,31} ROS damage cells through various mechanisms, such as protein inactivation and peroxidation of lipid membranes, which lead to DNA damage and the stimulation of some signaling pathways that lead to tissue damage. ROS can induce periodontal tissue destruction, which is associated with osteoclastic bone resorption.^{28,32} The NACHT-LRR-PYD domains-containing protein 3 (NALP3) inflammasome is a protein complex, including apoptosis-associated speck-like protein containing a caspase activation and recruitment domain (ASC) and caspase-1, and it is essential for the maturation of IL-1 β and IL-18.^{28,29} It is implicated not only in inflammatory disorders but also in numerous metabolic diseases. Clinical studies have shown that periodontitis is correlated with decreased total antioxidant status

and increased lipid peroxidation in gingival crevicular fluid, saliva, or blood.³³⁻³⁶

Drinking HRW is an alternative delivery of molecular hydrogen. It can increase the concentration of molecular hydrogen in blood and tissues.³⁷⁻⁴⁰ Clinical and animal studies have demonstrated that drinking HRW provides health benefits, such as the serum lipid profiles of those at risk for metabolic syndrome. Molecular hydrogen is considered a novel antioxidant that can reduce oxidative damage. Drinking HRW can suppress ligature-induced periodontal inflammation in a rat model (Kasuyama et al., 2011)²², anti-aging effects on periodontal oxidative damage (Tomofuji et al., 2014)²⁶, and enhanced the effects of non-surgical periodontal treatment, thus improving periodontitis (Azuma et al., 2015)²³. On the other hand, drinking HW suppressed the effects of a high-fat diet on body weight gain and showed lower serum and gingival 8-OHdG compared with the obese rats. It is feasible that HW suppresses obesity, which in turn might inhibit a systemic increase in oxidative stress, including gingival oxidative stress¹⁹.

For T2DM, drinking HRW can suppress the increase in glucose, total cholesterol, oxidative stress, and inflammation. Moreover, HRW also ameliorates hyperglycemia-induced liver, kidney, and spleen dysfunction, so patients with T2DM may improve their condition by supplementing HRW as daily drinking water (Zheng, 2021). Besides that, high concentration HRW would improve the various biomarkers of metabolic syndrome that are usually involved in the development of cardiovascular disease, namely dyslipidemia (HDL, LDL, VLDL, TG), inflammation (TNF- α , IL-6, CRP), oxidative stress (MDA, TBARS, DNA conjugates, vitamins E and C), and hyperglycemia (glucose, HbA1c). High-concentration HRW improved several biomarkers of cardiometabolic health in mid-age men and women with metabolic syndrome, including BMI, WHR, resting HR, blood lipids, glucose, inflammation, and redox homeostasis (Lebaron, 2020)²⁸.

The experimental and clinical studies have shown that animals or humans can breathe hydrogen or drink or inject HRW to protect the heart, brain, liver, kidney, lung, and small intestine from ischemia/reperfusion oxidative injury or an inflammatory injury after cardiac organ transplantation by decreased levels of serum MDA, IL-1, IL-6, and TNF- α . The potential biological effects of hydrogen in sports have drawn much attention from researchers in sports science. The beneficial protective effects of

hydrogen-rich water on the body have been gradually confirmed in animal and human experiments (Sha et al., 2018).²⁹

The effects of HRW on the antioxidant system have mostly been tested in in vitro or animal models. The antioxidant activity of HRW in the health sector was observed through a comprehensive analysis of oxidative stress biomarkers, blood immune cell profiles, and gene expression. Consumption of HRW for four weeks can induce a substantial increase in antioxidants and decrease oxidative stress. Research shows HRW significantly reduces the frequency of apoptotic cells. HRW suppresses the expression of genes involved in TLR / NF- κ B signaling. As a result, the level of pro-inflammatory cytokine transcripts is significantly decreased.⁴⁰⁻⁴²

Hydrogen can dissolve in water up to 1.6 ppm at one atmospheric pressure. Dissolved hydrogen concentrations vary widely depending on the machinery used in the manufacture, container, subsequent storage conditions, and other factors.⁴³⁻⁴⁶ This difference may have a significant effect on the efficacy of HRW. Zhou et al. (2019) showed that the higher the concentration of HRW, the faster the wound heals, and significant reductions were observed in IL-6 levels at the end of 1, 3, and 4 weeks.³⁴

It has been reported that antioxidants exert beneficial effects in diabetic mice, preserving in vivo β -cells function. The administration of electrolyzed reduced water to a mouse model of T2DM improved islet β -cells function, thus increasing circulating insulin release and enhanced

insulin sensitivity in both type 1 and type 2 diabetes (Kim, 2017).²⁴ The precise mechanisms by which antioxidant supplementation causes these beneficial effects on β -cells function in diabetes are complex. As hydrogen can readily pass across the cell membrane, consumption of hydrogen-rich water may affect intracellular events, such as protecting DNA from damage by ROS, thereby influencing gene transcription.^{25,28}

Studies show that uncontrolled DM can affect periodontal conditions that will affect orthodontic treatment outcomes by changing bone remodeling. Orthodontic appliances can facilitate plaque build-up, which can worsen periodontal disease. Experimental studies show that diabetes can transform bone remodeling and poor oral hygiene, which synergistically affect the detrimental effect of periodontal disease. One of the pro-inflammatory biomarkers in orthodontic treatment and periodontal health is interleukin.^{47,48}

Thus far, many reports have confirmed that consumption of HRW reduces oxidative stress in various disease models and clinical tests. Clinical tests revealed that drinking HRW reduced oxidative stress markers in patients with type 2 diabetes or subjects with potential metabolic syndrome and influenced glucose and cholesterol metabolism. Various studies regarding the effect of HRW on the disease by reducing inflammatory biomarkers such as interleukins and lowering blood glucose levels in DM patients in the presence of antioxidant effects lead us to research whether HRW can affect the orthodontic tooth movement in DM patients.

CONCLUSION

The results showed that long-term consumption of hydrogen-rich water exerts certain antioxidants for oxidative gingival stress and anti-inflammatory effects by decreasing interleukin and decreasing blood glucose levels for DM patients.

REFERENCES

- [1]. Al-Maskari AY, Al-Maskari MY, Al-Sudairy S. Oral manifestations and complications of diabetes mellitus: a review. Sultan Qaboos Univ Med J. 2011; 11(2): 179-186.
- [2]. Compston J. Type 2 diabetes mellitus and bone. J Intern Med. 2018; 283(2): 140-153.
- [3]. Preshaw PM, Alba AL, Herrera D, Jepsen S, Konstantinidis A, Makrilakis K, Taylor R. Periodontitis and diabetes: A two-way relationship. Diabetologia. 2012; 55(1): 21-31.
- [4]. Hernandez APR, Corona MLM, Lpyola APP, Solis CEM, Fyvie LAX. Subgingival microbiota of mexicans with type 2 diabetes with different periodontal and metabolic Conditions. Int J Environ Res Public Health. 2019; 16: 3184.
- [5]. Ferreira CL, Rocha VC, Silva Ursi WJ, et al. Periodontal response to orthodontic tooth movement in diabetes-induced rats with or

- without periodontal disease. *J Periodontol*. 2018; 89: 341-350.
- [6]. Santamaria-Jr M, Bagne L, Zaniboni E, Santamaria MP, Jardini MAN, Felonato M, Dos Santos GMT, Mendonça FAS, Esquisatto MAM. Diabetes mellitus and periodontitis: Inflammatory response in orthodontic tooth movement. *Orthod Craniofac Res*. 2020; 23(1): 27-34.
- [7]. Zhou X, Zhang W, Liu X, Zhang W, Li Y. Interrelationship between diabetes and periodontitis: role of hyperlipidemia. *Arch Oral Biol*. 2015; 60(4): 667-674.
- [8]. Graves DT, Ding Z, Yang Y. The impact of diabetes on periodontal diseases. *Periodontol 2000*. 2020; 82(1): 214-224.
- [9]. Wu YY, Xiao E, Graves DT. Diabetes mellitus related bone metabolism and periodontal disease. *Int J Oral Sci*. 2015; 7(2): 63-72.
- [10]. Chauhan N, Parikh T, Patel S, Shah A, Pandya P, Shah K. Diabetes mellitus, a myth in orthodontics?. *Int J Prev Clin Dent Res*. 2018; 5: 24-8.
- [11]. Matsumoto Y, Sringkarnboriboon S, Ono T. Proinflammatory mediators related to orthodontically induced periapical root resorption in rat mandibular molars. *Eur J Orthod*. 2017; 39(6): 686-691.
- [12]. Maedler K, Dharmadhikari G, Schumann DM, Størting J. Interleukin-targeted therapy for metabolic syndrome and type 2 diabetes. *Handb Exp Pharmacol*. 2011; (203): 257-78.
- [13]. Zhang J, Liu X, Wan C, Liu Y, Wang Y, Meng C, Zhang Y, Jiang C. NLRP3 inflammasome mediates M1 macrophage polarization and IL-1 β production in inflammatory root resorption. *J Clin Periodontol*. 2020; 47(4): 451-460.
- [14]. Napoli N, Chandran M, Pierroz DD, Abrahamsen B, Schwartz AV, Ferrari SL; IOF Bone and Diabetes Working Group. Mechanisms of diabetes mellitus-induced bone fragility. *Nat Rev Endocrinol*. 2017;13(4): 208-219.
- [15]. Braga SM, Taddei SR, Andrade I Jr, Queiroz-Junior CM, Garlet GP, Repeke CE, Teixeira MM, da Silva TA. Effect of diabetes on orthodontic tooth movement in a mouse model. *Eur J Oral Sci*. 2011; 119(1):7-14.
- [16]. Baeza M, Morales A, Cisterna C, Cavalla F, Jara G, Isamitt Y, Pino P, Gamonal J. Effect of periodontal treatment in patients with periodontitis and diabetes: systematic review and meta-analysis. *J Appl Oral Sci*. 2020; 28: e20190248.
- [17]. Shafiq HB, Amin U, Nawaz S. Comparative analysis of various antimicrobial agents present in locally available mouthwashes against oral pathogens. *Pak J Pharm Sci*. 2018 Sep;31(5): 1881-1887.
- [18]. Asada R, Tazawa K, Sato S, Miwa N. Effects of hydrogen-rich water prepared by alternating-current-electrolysis on antioxidant activity, DNA oxidative injuries, and diabetes-related markers. *Med Gas Res*. 2020;10(3): 114-121.
- [19]. Yoneda T, Tomofuji T, Kunitomo M, Ekuni D, Irie K, Azuma T, Machida T, Miyai H, Fujimori K, Morita M. Preventive Effects of Drinking Hydrogen-Rich Water on Gingival Oxidative Stress and Alveolar Bone Resorption in Rats Fed a High-Fat Diet. *Nutrients*. 2017; 9(1): 64.
- [20]. Tamaki N, Orihuela-Campos RC, Fukui M, Ito HO. Hydrogen-Rich Water Intake Accelerates Oral Palatal Wound Healing via Activation of the Nrf2/Antioxidant Defense Pathways in a Rat Model. *Oxid Med Cell Longev*. 2016; 2016: 5679040.
- [21]. Kajiyama S, Hasegawa G, Asano M, Hosoda H, Fukui M, Nakamura N, Kitawaki J, Imai S, Nakano K, Ohta M, Adachi T, Obayashi H, Yoshikawa T. Supplementation of hydrogen-rich water improves lipid and glucose metabolism in patients with type 2 diabetes or impaired glucose tolerance. *Nutr Res*. 2008; 28(3): 137-143.
- [22]. Kasuyama K, Tomofuji T, Ekuni D, Tamaki N, Azuma T, Irie K, Endo Y, Morita M. Hydrogen-rich water attenuates experimental periodontitis in a rat model. *J Clin Periodontol*. 2011; 38(12): 1085-1090.
- [23]. Azuma T, Yamane M, Ekuni D, Kawabata Y, Kataoka K, Kasuyama K, Maruyama T, Tomofuji T, Morita M. Drinking hydrogen-rich water has additive effects on non-surgical periodontal treatment of improving periodontitis: A pilot study. *Antioxidants (Basel)*. 2015; 4(3): 513-522.
- [24]. Kim J, Lee HJ, Hong SH. Inhibition of streptococcal biofilm by hydrogen water. *J Dent*. 2017; 58: 34-39.
- [25]. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med*. 2009;151(4): 264-9.
- [26]. Tomofuji T, Kawabata Y, Kasuyama K, Endo Y, Yoneda T, Yamane M, Azuma T, Ekuni D, Morita M. Effects of hydrogen-rich water on

- aging periodontal tissues in rats. *Sci Rep*. 2014; 4: 5534.
- [27]. Zheng M, Yu H, Xue Y, Yang T, Tu Q, Xiong K, Deng D, Lu L, Huang N. The protective effect of hydrogen-rich water on rats with type 2 diabetes mellitus. *Mol Cell Biochem*. 2021.
- [28]. LeBaron TW, Singh RB, Fatima G, Kartikey K, Sharma JP, Ostojic SM, Gvozdzakova A, Kura B, Noda M, Mojto V, Niaz MA, Slezak J. The effects of 24-week, high-concentration hydrogen-rich water on body composition, blood lipid profiles and inflammation biomarkers in men and women with metabolic syndrome: a randomized controlled trial. *Diabetes Metab Syndr Obes*. 2020;13: 889-896.
- [29]. Sha JB, Zhang SS, Lu YM, Gong WJ, Jiang XP, Wang JJ, Qiao TL, Zhang HH, Zhao MQ, Wang DP, Xia H, Li ZW, Chen JL, Zhang L, Zhang CG. Effects of the long-term consumption of hydrogen-rich water on the antioxidant activity and the gut flora in female juvenile soccer players from Suzhou, China. *Med Gas Res*. 2019; 8(4): 135-143.
- [30]. Kajisa T, Yamaguchi T, Hu A, Suetake N, Kobayashi H. Hydrogen water ameliorates the severity of atopic dermatitis-like lesions and decreases interleukin-1 β , interleukin-33, and mast cell infiltration in NC/Nga mice. *Saudi Med J*. 2017; 38(9): 928-933.
- [31]. Yamasaki M, Miyazono M, Yoshihara M, Suenaga A, Mizuta M, Fukuda M, Rikitake S, Ikeda Y. Effects of hydrogen-rich water in a rat model of polycystic kidney disease. *PLoS One*. 2019; 14(4): e0215766.
- [32]. Zhang J, Liu X, Wan C, Liu Y, Wang Y, Meng C, Zhang Y, Jiang C. NLRP3 inflammasome mediates M1 macrophage polarization and IL-1 β production in inflammatory root resorption. *J Clin Periodontol*. 2020; 47(4): 451-460.
- [33]. Yang Y, Liu PY, Bao W, Chen SJ, Wu FS, Zhu PY. Hydrogen inhibits endometrial cancer growth via a ROS/NLRP3/caspase-1/GSDMD-mediated pyroptotic pathway. *BMC Cancer*. 2020; 20(1): 28.
- [34]. Zhou P, Lin B, Wang P, Pan T, Wang S, Chen W, Cheng S, Liu S. The healing effect
- [44]. Ostojic SM. Molecular hydrogen in sports medicine: new therapeutic perspectives. *Int J Sports Med*. 2015; 36(4): 273-279.
- [45]. Tian R, Hou Z, Hao S, Wu W, Mao X, Tao X, Lu T, Liu B. Hydrogen-rich water attenuates brain damage and inflammation after
- of hydrogen-rich water on acute radiation-induced skin injury in rats. *J Radiat Res*. 2019; 60(1): 17-22.
- [35]. Wu Q, Zhang J, Wan Y, Song S, Zhang Y, Zhang G, Liu C, Fu J. Hydrogen water alleviates lung injury induced by one-lung ventilation. *J Surg Res*. 2015; 199(2): 664-670.
- [36]. Guo Q, Yin X, Qiao M, Jia Y, Chen D, Shao J, LeBaron TW, Gao Y, Shi H, Jia B. Hydrogen-Rich Water Ameliorates Autistic-Like Behavioral Abnormalities in Valproic Acid-Treated Adolescent Mice Offspring. *Front Behav Neurosci*. 2018; 12: 170.
- [37]. Kamimura N, Nishimaki K, Ohsawa I, Ohta S. Molecular hydrogen improves obesity and diabetes by inducing hepatic FGF21 and stimulating energy metabolism in db/db mice. *Obesity (Silver Spring)*. 2011; 19(7): 1396-1403.
- [38]. Li J, Zeng Z, Zhao Y, Jing D, Tang C, Ding Y, Feng X. Effects of low-intensity pulsed electromagnetic fields on bone microarchitecture, mechanical strength and bone turnover in type 2 diabetic db/db mice. *Sci Rep*. 2017; 7(1): 10834.
- [39]. Yang L, Li D, Chen S. Hydrogen water reduces NSE, IL-6, and TNF- α levels in hypoxic-ischemic encephalopathy. *Open Med (Wars)*. 2016; 11(1): 399-406.
- [40]. Zhang Y, Su WJ, Chen Y, Wu TY, Gong H, Shen XL, Wang YX, Sun XJ, Jiang CL. Effects of hydrogen-rich water on depressive-like behavior in mice. *Sci Rep*. 2016; 6: 23742.
- [41]. Tamasawa A, Mochizuki K, Hariya N, Saito M, Ishida H, Doguchi S, Yanagiya S, Osonoi T. Hydrogen gas production is associated with reduced interleukin-1 β mRNA in peripheral blood after a single dose of acarbose in Japanese type 2 diabetic patients. *Eur J Pharmacol*. 2015; 762: 96-101.
- [42]. Kawamura T, Higashida K, Muraoka I. Application of Molecular Hydrogen as a Novel Antioxidant in Sports Science. *Oxid Med Cell Longev*. 2020; 2020: 2328768.
- [43]. Ichihara M, Sobue S, Ito M, Ito M, Hirayama M, Ohno K. Beneficial biological effects and the underlying mechanisms of molecular hydrogen - comprehensive review of 321 original articles. *Med Gas Res*. 2015; 5: 12.
- traumatic brain injury in rats. *Brain Res*. 2016;1637: 1-13.
- [46]. Ekuni D, Tomofuji T, Endo Y, Kasuyama K, Irie K, Azuma T, Tamaki N, Mizutani S, Kojima A, Morita M. Hydrogen-rich water prevents lipid deposition in the descending

- aorta in a rat periodontitis model. *Arch Oral Biol.* 2012; 57(12): 1615-1622.
- [47]. Villarino ME, Lewicki M, Ubios AM. Bone response to orthodontic forces in diabetic Wistar rats. *Am J Orthod Dentofacial Orthop.* 2011;139(4 Suppl): S76-82.
- [48]. Gkantidis N, Christou P, Topouzelis N. The orthodontic-periodontic interrelationship in integrated treatment challenges: a systematic review. *J Oral Rehabil.* 2010; 37(5): 377-390.