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Molecular hydrogen improves obesity and diabetes by inducing hepatic FGF21 and stimulating energy metabolism in db/db mice.

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Abstract

Recent extensive studies have revealed that molecular hydrogen (H(2)) has great potential for improving oxidative stress-related diseases by inhaling H(2) gas, injecting saline with dissolved H(2), or drinking water with dissolved H(2) (H(2)-water); however, little is known about the dynamic movement of H(2) in a body. First, we show that hepatic glycogen accumulates H(2) after oral administration of H(2)-water, explaining why consumption of even a small amount of H(2) over a short span time efficiently improves various disease models. This finding was supported by an in vitro experiment in which glycogen solution maintained H(2). Next, we examined the benefit of ad libitum drinking H(2)-water to type 2 diabetes using db/db obesity model mice lacking the functional leptin receptor. Drinking H(2)-water reduced hepatic oxidative stress, and significantly alleviated fatty liver in db/db mice as well as high fat-diet-induced fatty liver in wild-type mice. Long-term drinking H(2)-water significantly controlled fat and body weights, despite no increase in consumption of diet and water. Moreover, drinking H(2)-water decreased levels of plasma glucose, insulin, and triglyceride, the effect of which on hyperglycemia was similar to diet restriction. To examine how drinking H(2)-water improves obesity and metabolic parameters at the molecular level, we examined gene-expression profiles, and found enhanced expression of a hepatic hormone, fibroblast growth factor 21 (FGF21), which functions to enhance fatty acid and glucose expenditure. Indeed, H(2) stimulated energy metabolism as measured by oxygen consumption. The present results suggest the potential benefit of H(2) in improving obesity, diabetes, and metabolic syndrome.

Metabolism & Diabetes

Supplementation of hydrogen-rich water improves lipid and glucose metabolism in patients with type 2 diabetes or impaired glucose tolerance

Type 2 diabetes (adult-onset diabetes) is a disease in which there are high levels of sugar (glucose) in the blood. It is the most common form of diabetes. In type 2 diabetes, either the body does not produce enough insulin or the cells ignore the insulin. Insulin is necessary for the body to be able to use glucose for energy. Impaired Glucose Tolerance (IGT) is the condition of having blood glucose levels that are higher than normal, but below the level of a person with diabetes. It is a pre-diabetic state.

Scientists tested the effects of drinking hydrogen-rich water in 30 human patients with Type 2 diabetes mellitus and 6 with IGT. The patients drank about 4 cups of hydrogen-rich water each day for 8 weeks, or a placebo of pure water. They found that several biomarkers of diabetes (properties of blood and urine that indicate the presence or severity of diabetes) were improved by drinking hydrogen-rich water. In 4 of the 6 patients with IGT, drinking hydrogen-rich water changed the results of the medical test for IGT back to normal. The scientists conclude that drinking hydrogen-rich water may have a beneficial role in preventing Type 2 diabetes and insulin resistance.

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Effectiveness of Hydrogen rich water on antioxidant status of subjects with potential metabolic syndrome-an open label pilot study

Metabolic syndrome is a combination of one or more medical disorders including:

- Obesity
- Insulin resistance
- Hyperglycemia (high blood sugar)
- Hypertension (high blood pressure)
- High concentration of LDL cholesterol (sometimes called "bad" cholesterol
- Low concentration of HDL cholesterol (or "good" cholesterol)

Metabolic syndrome increases the risk of developing cardiovascular disease and diabetes. Oxidative stress plays a major role in the development of metabolic syndrome.

In this study, 20 human patients with potential metabolic syndrome drank 1.5 to 2 liters (6 to 8 cups) of hydrogen rich water daily for 8 weeks. Since this was an "open label" study, no placebo was given. The patients had improved oxidative stress biomarkers, improved HDL cholesterol levels, and improved total cholesterol ratios. Blood glucose levels were not affected.

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Molecular hydrogen improves obesity and diabetes by inducing hepatic FGF21 and stimulating energy metabolism in db/db mice

Db/db mice are specially bred to be a model of obesity, diabetes and dyslipidemia (abnormal amounts of cholesterol or fat in the blood.) These mice are obese by the age of 3 or 4 weeks old. They are insulin resistant and have impaired glucose tolerance. On the right side of this page is a photo showing a db/db mouse next to a regular mouse.

The mice in this study were given hydrogen rich water from 6 weeks of age, *ad libitum* (as much as they wanted to drink.) The results showed that consuming hydrogen rich water:

- reduces oxidative stress in the liver and improves fatty liver
- suppressed body-weight gain and reduced blood glucose and triglyceride levels
- shows a similar effect to diet restriction
- increases the level of FGF21 (a protein that regulates energy expenditure, protects from obesity caused by overeating, and lowers blood glucose and triglyceride levels) in the liver
- stimulates energy metabolism

Another result of this study was to explain how the body stores hydrogen. Scientists had struggled to understand how ingesting the small amount of hydrogen contained in hydrogen rich water could have such significant clinical effects. This study showed that hydrogen is accumulated and reserved in the liver by attaching to glycogen molecules.
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Effects of hydrogen-rich water on abnormalities in a SHR.Cg-*Lepr*^{cp}/NDmcr rat -- a metabolic syndrome rat model

Abstract
Background: Hydrogen (H2), a potent free radical scavenger, selectively reduces the hydroxyl radical, which is the most cytotoxic of the reactive oxygen species (ROS). An increase in oxygen free radicals induces oxidative stress, which is known to be involved in the development of metabolic syndrome. Therefore, we investigated whether hydrogen-rich water (HRW) affects metabolic abnormalities in the metabolic syndrome rat model, SHR.Cg-Leprcp/ NDmcr (SHR-cp).
Methods: Male SHR-cp rats (5 weeks old) were divided into 2 groups: an HRW group was given oral HRW for 16 weeks, and a control group was given distilled water. At the end of the experiment, each rat was placed in a metabolic cage for 24 h, fasted for 12 h, and anesthetized; the blood and kidneys were then collected.
Results: Sixteen weeks after HRW administration, the water intake and urine flow measured in the metabolic cages were significantly higher in the HRW group than in the control group. The urinary ratio of albumin to creatinine was significantly lower and creatinine clearance was higher in the HRW group than in the control group. After the 12-h fast, plasma urea nitrogen and creatinine in the HRW group were significantly lower than in the control group. The plasma total antioxidant capacity was significantly higher in the HRW group than in the control group. The glomerulosclerosis score for the HRW group was significantly lower than in the control group, and a significantly positive correlation was observed between this score and plasma urea nitrogen levels.
Conclusion: The present findings suggest that HRW conferred significant benefits against abnormalities in the metabolic syndrome model rats, at least by preventing and ameliorating glomerulosclerosis and creatinine clearance.

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