

Role of molecular hydrogen in obesity treatment: modulation of GLP-1, irisin, and PGC-1 α for improved metabolism

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The increasing prevalence of obesity and non-communicable diseases has become a major global health concern, contributing to significant morbidity and mortality rates. These conditions not only burden healthcare systems but also affect the individual's quality of life worldwide. As these challenges continue to grow, there is a pressing need to explore treatment options that are effective, affordable, and widely accessible. While traditional pharmaceutical interventions have shown benefits, they often come with limitations, including side effects and/or high costs, highlighting the importance of investigating alternative or complementary approaches to address these complex health issues. Dietary supplements offer a promising complementary approach through their impact on metabolic pathways. Recent advances in understanding metabolic regulation, including the role of gut hormones such as glucagon-like peptide-1 (GLP-1), have opened new possibilities for innovative therapeutic approaches. In alignment with this objective, we propose molecular hydrogen (H₂, dihydrogen) as a promising adjunct supplementary strategy for managing obesity and related non-communicable diseases.

Dihydrogen is a medical gas with extensively documented antioxidant, anti-inflammatory, and signaling properties, validated in over 1000 studies across more than 100 disease models,¹ and has shown significant efficacy in improving clinical endpoints and surrogate markers from metabolic diseases to chronic systemic inflammatory disorders.² For example, a six-month randomized clinical trial involving 1088 patients with type 2 diabetes mellitus (T2DM) receiving standard anti-diabetic therapy, with or without supplemental hydrogen inhalation, demonstrated that long-term hydrogen administration significantly improved key metabolic parameters. Specifically, patients in the hydrogen group exhibited reductions in HbA1c, fasting glucose, and total cholesterol levels, alongside improvements in HOMA-IR and HOMA- β indices, highlighting the potential of hydrogen therapy to affect metabolic health.³ In

a related context, our research team conducted a meta-analysis that showcased the potential of hydrogen-rich water (HRW) in the context of blood lipid profiles within clinical populations.⁴ Our findings demonstrated a significant decrease in total cholesterol, low-density lipoprotein, and triglyceride levels following HRW intervention. These results highlight the critical role of dihydrogen in metabolic health, suggesting that H₂ not only modulates lipid profiles but also might influence insulin and ghrelin—two key hormones essential for glucose regulation.

One of the primary mechanisms explaining the effects of dihydrogen on insulin involves the modulation of peroxisome proliferator-activated receptor gamma coactivator-1 alpha (PGC-1 α). For instance, earlier investigations indicated that administering HRW to male db/db diabetic mice over a two-week period increased the expression of PGC-1 α , significantly affecting their metabolic profiles.⁵ Furthermore, the potential modulation of PGC-1 α expression by HRW may also be linked to irisin, a myokine released into the bloodstream through the cleavage of fibronectin type III domain-containing protein 5 (FNDC5). PGC-1 α expression in muscle stimulates an increase in FNDC5 expression, directly affecting irisin circulation.⁶ Irisin enhances the metabolic activity of adipocytes and myocytes while exerting protective effects against obesity, insulin resistance, and NAFLD, with these metabolic benefits linked to inflammatory markers. This suggests that irisin may regulate the inflammatory response, and there is a probability that this irisin-related mechanism partially explains H₂'s anti-inflammatory and antioxidative effects. A possible connection between H₂ and irisin could significantly change the perspective in dihydrogen applications.

Research on therapeutics targeting GLP-1 has gained significant attention in recent years. Treatment with GLP-1 receptor agonists has been shown to confer substantial benefits, including improved cardiovascular outcomes, reduced mortality, and better kidney function in patients with T2DM.⁷ Additionally, GLP-1

receptor agonists promote weight loss in overweight and obese individuals, regardless of the presence of T2DM.⁸ Consequently, searching for therapies or supplements capable of modulating GLP-1 secretion has become a major focus in metabolic research. Dihydrogen might influence GLP-1 secretion through multiple pathways, including those involving PGC-1 α and gut microbiota, potentially enhancing its effects. PGC-1 α is primarily known for its involvement in mitochondrial biogenesis, fatty acid oxidation, and energy homeostasis across various tissues such as the liver, skeletal muscle, and adipose tissue. Its activation can influence metabolic pathways that may intersect with those modulated by GLP-1. For instance, GLP-1's effects on improving hepatic fat accumulation might involve pathways that include factors related to mitochondrial function and fat metabolism, areas where PGC-1 α plays a key role.⁹ Additionally, GLP-1 has been shown to regulate the mitochondrial protective gene PGC-1 α .¹⁰ GLP-1 increases the expression of PGC-1 α by downregulating miR-23a, thereby inhibiting hepatocyte apoptosis. Moreover, it enhances the activity of mitochondrial uncoupling protein 2, which mitigates apoptosis by reducing mitochondrial stress, further emphasizing the interconnected roles of these pathways in cellular protection.¹⁰ Conversely, H₂ plays a role in modulating gut microbiota, thereby indirectly influencing GLP-1 secretion. It was shown that short-chain fatty acids (SCFAs) could modulate gut hormone release, including triggering the secretion of GLP-1.¹¹ Certain gut bacteria stimulate GLP-1 release through the production of SCFAs like butyrate, which are known to activate GLP-1-producing L-cells in the intestine.¹¹ A previous study found that 12 weeks of dihydrogen supplementation altered SCFAs in 10 middle-aged overweight individuals (five women), specifically propionic and butyric acid.¹² By promoting a healthy gut microbial environment, H₂ may enhance SCFA production, thereby supporting GLP-1 secretion and improving metabolic regulation. As evidence continues to emerge, dihydrogen's role in modulating GLP-1 secretion via anti-inflammatory effects, gut microbiota modulation, and enhancement of PGC-1 α presents a promising direction in metabolic research.

In summary, we propose that H₂ could serve as a valuable adjunct therapy for individuals with metabolic conditions (**Figure 1**). However, further fundamental and experimental research is essential to elucidate its mechanisms and expand its therapeutic potential for managing conditions such as T2DM, obesity, and metabolic syndrome.

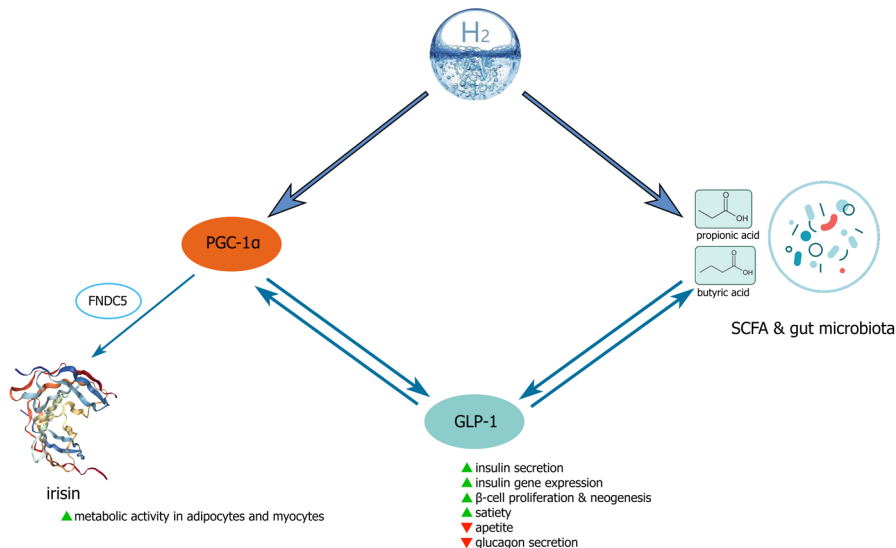


Figure 1 | Molecular hydrogen-mediated modulation of PGC-1α, irisin, and GLP-1 expression.

The effects of molecular hydrogen (dihydrogen) on metabolic health are multifaceted. Firstly, dihydrogen enhances the activity of peroxisome proliferator-activated receptor gamma coactivator 1-α (PGC-1α), which subsequently promotes the production of irisin through the fibronectin type III domain-containing protein 5 (FND5) pathway. Moreover, PGC-1α forms a positive feedback loop with glucagon-like peptide-1 (GLP-1), collectively exerting beneficial effects on metabolic health. Additionally, dihydrogen positively influences gut microbiota by promoting the production of short-chain fatty acids (SCFAs), specifically butyric acid and propionic acid. These SCFAs have been shown to enhance GLP-1 secretion, creating a positive feedback loop that further supports metabolic regulation. Created with Adobe Photoshop CS6.

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Date of submission: December 17, 2024

Date of decision: January 3, 2025

Date of acceptance:

Date of web publication: February 08, 2025

<https://doi.org/10.4103/mgr.MEDGASRES-D-24-00146>

How to cite this article: Todorović N, Kuzmanovic J, Javorac D, Ostojic SM. Role of molecular hydrogen in obesity treatment: modulation of GLP-1, irisin, and PGC-1α for improved metabolism. *Med Gas Res.* 2025;15(0):000-000.

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