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**EDITORIAL**

- 138 Exercise and glucagon-like peptide-1: Does exercise potentiate the effect of treatment?

*Hamasaki H*

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## Exercise and glucagon-like peptide-1: Does exercise potentiate the effect of treatment?

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### Abstract

Recently, glucagon-like peptide-1 (GLP-1) receptor agonists have become a cornerstone for the treatment of obese patients with type 2 diabetes (T2D), exhibiting favorable effects on the cardiovascular outcome. In

T2D, impaired GLP-1 secretion/function is observed, and gut microbiota dysbiosis is related to the GLP-1 resistance. Prior research has revealed that exercise increases GLP-1 levels in healthy and obese individuals; however, the efficacy of exercise on GLP-1 levels in patients with T2D remains unclear. Exercise may improve GLP-1 resistance rather than GLP-1 secretion in patients with T2D. Exercise increases the gut microbiota diversity, which could contribute to improving the GLP-1 resistance of T2D. Furthermore, the gut microbiota may play a role in the correlation between exercise and GLP-1. The combination of exercise and GLP-1-based therapy may have a synergistic effect on the treatment of T2D. Although the underlying mechanism remains unknown, exercise potentiates the efficacy of GLP-1 receptor agonist treatment in patients with T2D.

**Key words:** Type 2 diabetes; Exercise; Glucagon-like peptide-1; Gut microbiota; Myokine

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**Core tip:** The impact of exercise on glucagon-like peptide-1 (GLP-1) receptor agonists in patients with type 2 diabetes (T2D) remains unclear. Exercise could potentiate the effect of GLP-1 receptor agonists treatment and play a vital role in ameliorating GLP-1 resistance by improving gut microbiota dysbiosis and reducing the ectopic fat in patients with T2D.

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Recently, the use of glucagon-like peptide-1 (GLP-1)

receptor agonists has become an essential treatment in obese patients with type 2 diabetes (T2D). The efficacy of GLP-1 receptor agonists has been established for all components of metabolic syndrome and hyperglycemia, which accounts for favorable effects on the cardiovascular outcome<sup>[1]</sup>. GLP-1 is secreted by the intestinal L cells, promotes satiety, inhibits gastric emptying, stimulates insulin secretion, and suppresses glucagon secretion in response to food consumption<sup>[2]</sup>. In patients with T2D, the incretin effect is severely diminished, suggesting that altered GLP-1 secretion/function is associated with T2D pathophysiology. The abnormality of the incretin effect in T2D could be attributed to GLP-1 resistance in  $\beta$ -cells<sup>[2]</sup>.

Several studies have established a marked correlation between the composition of gut microbiota and the pathophysiology of diabetes and obesity<sup>[3]</sup>. Grasset *et al*<sup>[4]</sup> reported that gut microbiota dysbiosis caused GLP-1 resistance in obese and diabetic mice. In addition, the relative abundance of Lactobacilli was decreased in GLP-1-resistant mice and positively correlated with the ileum GLP-1 receptor and neuronal nitric oxide synthase mRNA concentrations. Furthermore, the relative abundance of Bacteroidales, Burkholderiales, and Clostridiales was increased in diabetic mice, and that of Bacteroidales negatively correlated with the ileum GLP-1 receptor and neuronal nitric oxide synthase mRNA concentrations. Although the underlying mechanism by which gut microbiota dysbiosis induces GLP-1 resistance in the enteric nervous system remains unclear, this study suggests that the gut-brain axis plays a significant role in GLP-1-activated insulin secretion and gastric emptying.

In contrast, exercise therapy is essential for managing T2D<sup>[5]</sup>, and regular exercise offers benefits for cardiovascular, immunological, and neural systems<sup>[6]</sup>. Reportedly, exercise increases the diversity of the gut microbiota and alters the composition of microbiota at the phylum, family, and genus levels in humans, and could regulate the immune and neural function of the gut<sup>[7]</sup>.

Studies have reported that moderate-intensity (50%-75% maximal oxygen uptake) and high-intensity (85%-90% maximal heart rate) acute exercise increases GLP-1 levels compared with controls in healthy and obese individuals<sup>[8-11]</sup>. In addition, a 12-wk supervised chronic exercise program was reported to increase postprandial GLP-1 levels in overweight/obese individuals<sup>[12]</sup>. Although the effect of light-intensity exercise on GLP-1 levels remains unclear, regular exercise appears to increase GLP-1 levels irrespective of its intensity. However, few studies have investigated the efficacy of exercise on GLP-1 levels in patients with T2D. Lee *et al*<sup>[13]</sup> reported that a 12-wk high-intensity interval exercise training ( $\geq 80\%$  heart rate reserve) elevated GLP-1 levels compared with the energy expenditure-matched low-intensity exercise in adolescents with T2D. Conversely, Eshghi *et al*<sup>[14]</sup> demonstrated that moderate-intensity exercise (4.9 metabolic equivalents, 35 min) did not substantially increase the total GLP-1 levels

in patients with T2D, although metformin increased GLP-1 levels independent of exercise. A recent 16-wk, randomized, double-blind, placebo-controlled study reported that treatment using a GLP-1 receptor agonist, liraglutide, combined with exercise effectively improved glycemic control and resulted in weight loss<sup>[15]</sup>. The exercise program comprised 60-min supervised training, including high-intensity interval training and whole-body resistance training, for three times per week. Although no changes in GLP-1 levels were observed, exercise potentiated the effect of the GLP-1 receptor agonist treatment. The combination of exercise and GLP-1 receptor agonists enhances both the  $\beta$ -cell function and the peripheral insulin sensitivity. In addition, short-term vigorous aerobic exercise (85% maximal heart rate) was reported to decrease fasting GLP-1 levels, whereas GLP-1 responses to glucose were considerably increased in individuals with nonalcoholic fatty liver disease<sup>[16]</sup>. Although the impact of exercise on GLP-1 remains undetermined; Kullman *et al*<sup>[16]</sup> suggested that exercise improves GLP-1 resistance rather than increase GLP-1 secretion in patients with T2D.

GLP-1 resistance is caused by excessive visceral fat<sup>[17]</sup>, as well as gut microbiota dysbiosis<sup>[4]</sup>. In addition, physical inactivity is a potent risk factor for the accumulation of visceral fat, which is associated with systemic inflammation<sup>[18]</sup>. The skeletal muscle is an endocrine organ and releases various myokines, including interleukin (IL)-6, IL-8, and IL-15. Contracting the skeletal muscle during exercise exerts anti-inflammatory effects by myokines and reduces ectopic fat<sup>[18]</sup>. Heiskanen *et al*<sup>[19]</sup> recently reported that both sprint interval and moderate-intensity continuous training decreased pancreatic fat and improved the  $\beta$ -cell function in subjects with prediabetes and T2D. Although the authors did not evaluate the incretin effect in this study, they speculated that exercise can improve the  $\beta$ -cell function to read potentiating incretins and neural signals.

To date, the efficacy of exercise on the GLP-1 secretion/function is only partially investigated in patients with T2D. However, exercise appears to potentiate the effect of the GLP-1 receptor agonists treatment by ameliorating GLP-1 resistance. The role played by gut microbiota in causing GLP-1 resistance is a focus of attention; however, to our knowledge, no study has investigated the effect of exercise on GLP-1 resistance in association with the alteration of the gut microbiota. Notably, the precise adjustment of various confounding factors, such as diet, medications, comorbidities, and genetic factor, is challenging in human studies. Exercise also increases microbiota-derived short chain fatty acids (SCFA)<sup>[20]</sup> which have been shown to improve insulin sensitivity<sup>[21]</sup>. Short chain fatty acids interact with specific G-protein coupled receptors (GPR41 and GPR43) on the intestinal L-cells<sup>[22]</sup>, and increase GLP-1 secretion<sup>[23]</sup>. Exercise may improve GLP-1 secretion/function through the SCFA signaling mechanism. In addition, myokines are believed to play a vital role in mediating GLP-1 secretion/function during exercise. Although current



evidence is limited, a human study demonstrated that a GLP-1 receptor agonist, exenatide, treatment elevated irisin levels and enhanced the glycemic control in patients with T2D<sup>[24]</sup>. Nevertheless, further research is warranted in the future.

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