# Effect of Diet-Induced Obesity and Insulin Resistance on Gluconeogenesis and Glucagon Action

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## Abstract

Obesity is a major U.S. and global health problem that is correlated with insulin resistance and type 2 diabetes (T2D). Elevated blood glucagon levels have been associated with insulin resistant and T2D, indicating an important role glucagon may play in the pathophysiology of T2D. The purpose of this study was to determine whether insulin resistance and obesity increase hepatic glucagon action and gluconeogenesis in mice. It was hypothesized that hepatic glucose production would be higher in obese mice in response to glucagon compared to normal-weight mice. 6-week-old male C57BL6 mice were assigned to two groups, one fed with a high fat diet (HFD, $n = 9$), and the other with a low-fat diet (LFD, $n = 8$). Body composition, insulin action, gluconeogenesis, and glucagon action were evaluated after 20 weeks of dietary intervention. Body mass, fat mass, and % fat in HFD mice were significantly higher compared to LFD mice ($p < 0.001$), demonstrating that obesity was successfully induced in HFD mice. The average blood glucose levels during the insulin assisted glucose tolerance test were significantly higher in HFD compared to LFD mice ($p < 0.001$), demonstrating that the HFD mice were insulin resistant. The average blood glucose levels during pyruvate tolerance test were significantly higher in HFD compared to LFD mice ($p = 0.038$), demonstrating that gluconeogenesis is higher in HFD mice, independent of elevated insulin levels. The average blood glucose levels during the glucagon tolerance test were significantly higher in HFD compared to LFD mice ($p <0.001$), indicating that the gluconeogenesis pathway is more responsive to glucagon administration in diet-induced obese mice. A trend of increase in serum insulin concentration was observed in both HFD and LFD mice injected with glucagon. A trend of higher serum insulin concentration following a glucagon injection was observed in HFD mice compared to LFD mice. These findings suggest that gluconeogenesis and glucagon action are increased in obesity and insulin resistance. Additional studies are needed to determine if insulin resistance plays a role in the increased glucagon action.