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Insulin Resistance Alters Islet Morphology in Nondiabetic Humans

Type 2 diabetes is characterized by poor glucose uptake in metabolic tissues and manifests when insulin secretion fails to cope with worsening insulin resistance. In addition to its effects on skeletal muscle, liver, and adipose tissue metabolism, it is evident that insulin resistance also affects pancreatic β-cells. To directly examine the alterations that occur in islet morphology as part of an adaptive mechanism to insulin resistance, we evaluated pancreas samples obtained during pancreatoduodenectomy from nondiabetic subjects who were insulin-resistant or insulin-sensitive. We also compared insulin sensitivity, insulin secretion, and incretin levels between the two groups. We report an increased islet size and an elevated number of β- and α-cells that resulted in an altered β-cell–to–α-cell area in the insulin- resistant group. Our data in this series of studies suggest that neogenesis from duct cells and transdifferentiation of α-cells are potential contributors to the β-cell compensatory response to insulin resistance in the absence of overt diabetes.

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Insulin resistance, along with β-cell inadequacy, represent the key features in the pathogenesis of type 2 diabetes, and that both are essential for the full manifestation of the disease is generally accepted (1).

A feature that has been recognized in rodents (2,3) and humans (4–6) is the ability of the pancreas to compensate for insulin resistance by an increase in β-cell mass and insulin secretion. Indeed, β-cell mass is dynamic and capable of adapting to physiological and pathological conditions to maintain normoglycemia (7–9). Studies in humans suggest that the number and mass of β-cells increase in response to obesity; however, the time of onset of the increase and the precise origin of such new β-cells are still unknown (7). It is also evident that a failure of this ability of the β-cells to compensate for insulin resistance leads to progressive hyperglycemia and glucose toxicity (10) and to overt diabetes (11). A challenge to identifying the pathways and investigating the mechanisms that underlie compensatory changes in islets is the lack of longitudinal access to human tissue samples of appropriate quality for analyses coupled with accurate metabolic and hormonal profiling.

We took advantage of the unique opportunity to collect pancreas samples from patients undergoing surgical removal of a tumor of the ampulla of Vater to explore the hypothesis that insulin resistance directly contributes to adaptive changes in β-cell mass and function. To this end, we measured insulin sensitivity, insulin secretion,

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