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COMMENT ON ALARCON ET AL.

Pancreatic β-Cell Adaptive Plasticity in Obesity Increases Insulin Production but Adversely Affects Secretory Function. Diabetes 2016;65:438–450

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Alarcon et al. (1) recently demonstrated that β-cell insulin secretory dysfunction is rapidly restored by exposure of islets to low-normal glucose ex vivo in *db/db* mice. The authors allude to the potential clinical relevance for "transient β-cell rest" in type 2 diabetes (T2D). Could transient β-cell rest be accomplished by manipulating diet?

Lim et al. (2) have shown that a very low-calorie diet (~600 kcal/day) rapidly reverses most T2D-related metabolic dysfunction. After 1 week, fasting plasma glucose is normalized, fasting plasma insulin and C-peptide are reduced substantially, and the fasting rate of insulin secretion is lowered (i.e., evidence of β-cell rest). Stepwise hyperglycemic clamps showed that insulin secretory function was already improving after 1 week but took 8 weeks on the calorie-restricted diet to fully normalize, an effect linked to reduced pancreatic triglyceride levels. Thus, as little as 1 week of a very low-calorie diet in humans with T2D can relieve β-cell stress and achieve partial normalization of insulin secretory function, analogous to the restoration seen in islets from *db/db* mice exposed to 3 mmol/L glucose by Alarcon et al. (1).

Although reversal of T2D in individuals following a very low-calorie diet appears robust in some individuals (3), adherence to such extreme caloric restriction remains uncertain. Another strategy for providing β-cell rest may be to simply restrict dietary carbohydrates. Longer-term studies of low-carbohydrate diets clearly show profound effects at improving glucose control, but weight loss and triglyceride lowering (4) likely confound the interpretation of potential improvements in β-cell function. Accordingly, short-term (days to weeks) low-carbohydrate diet studies in humans with T2D could be used as a simple strategy to determine whether reducing insulin demand through diet can provide β-cell rest. β-Cell function and β-cell stress biomarkers could be key outcomes in such studies.

In summary, the data from Alarcon et al. (1) suggest that transient β-cell rest may hold therapeutic potential in T2D. Evidence from human studies is available to design practical interventions to test whether short-term low-calorie and/or carbohydrate-restricted diets, perhaps applied cyclically or intermittently, can provide transient β-cell rest to relieve insulin secretory demand and reverse β-cell dysfunction in T2D.

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