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Authors
Ritzel, Robert A
Butler, Alexandra E
Rizza, Robert A
et al.

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Relationship Between β-Cell Mass and Fasting Blood Glucose Concentration in Humans

ROBERT A. RITZEL, MD[1]
ALEXANDRA E. BUTLER, MD[1]
ROBERT A. RIZZA, MD[2]
JOHANNES D. VELDHUIS, MD[2]
PETER C. BUTLER, MD[1]

In type 2 diabetes there is a progressive defect of insulin secretion that precedes the development of hyperglycemia (1). This defect appears to be at least in part due to a deficit in β-cell mass (2–4). Several therapeutic strategies are now being proposed that may reverse the defect in β-cell mass in people with type 2 diabetes, for example glucagon-like peptide 1 or glucagon-like peptide 1–like surrogates (5). However, the relationship between β-cell mass and the blood glucose in humans is uncertain. Here we report the relative β-cell volume in pancreata obtained at autopsy from people with well-documented blood glucose concentrations in life.

RESEARCH DESIGN AND METHODS

— Mean β-cell volume, β-cell replication, and β-cell apoptosis for the case subjects included in this analysis have been reported previously (3). Here we now show the individual data points for blood glucose versus relative β-cell volume in obese case subjects who were nondiabetic, had impaired fasting glucose, or had type 2 diabetes. Pancreatic tissue was processed and immunostained for insulin, and the relative β-cell volume was quantified as previously described (3). The relative β-cell volume was used as a surrogate for β-cell mass since whole-pancreas weight is not available.

Selection of the study subjects from autopsy files was previously described (3). In brief, all case subjects included were obese (BMI >27 kg/m^2) and either nondiabetic (<110 mg/dl [6.1 mmol/l]) (n = 31, age 66.9 ± 15.2 years, BMI 36.4 ± 6.9 kg/m^2), had impaired fasting glucose (≥110 mg/dl [6.1 mmol/l] but <126 mg/dl [7.0 mmol/l]) (n = 19, age 63.1 ± 10.1 years, BMI 36.8 ± 8.6 kg/m^2), or were diabetic (≥126 mg/dl [7.0 mmol/l]) (n = 7, age 59.7 ± years, BMI 36.5 ± 5.3 kg/m^2). We only included people with type 2 diabetes who were not taking insulin or glucose-lowering oral medications, both of which would have influenced the measured blood glucose concentrations and the relationship of these with β-cell volume.

The relationship between fractional β-cell volume and fasting blood glucose concentration was analyzed by nonlinear regression analysis to establish the best monoexponential fit of the relationship between the fasting blood glucose (dependent variable) and the β-cell volume (independent variable); $y = \text{span} \times \exp(-k \times X) + \text{plateau}$ and the point of inflection of the hyperbole. ANOVA was used to test for the effect of β-cell volume on fasting blood glucose.

RESULTS

— There was a significant relationship between the β-cell volume and fasting blood glucose concentration, with a point of inflection at x = 1.1 ± 0.1%. This relationship is curvilinear (Fig. 1) so that β-cell deficiency beyond 1.1% is associated with a steep increase in blood glucose with each further decrement in β-cell mass.

CONCLUSIONS

— We report that in humans there is a curvilinear relationship between the relative β-cell volume (and presumably the β-cell mass) and the fasting blood glucose concentration. The present data reveal a narrow range of blood glucose over a wide range of fractional β-cell volume (up to ~10%) and then a much wider range of blood glucose values over a narrow range of volumes at low β-cell volumes, with the threshold set by the curve at ~1.1% defining that difference. The implications of these findings are that there is a much greater tolerance for variance in insulin sensitivity above this threshold and that below-the-threshold variance in insulin sensitivity and functional defects in insulin secretion have a much greater impact on blood glucose.

There are some important limitations with autopsy studies. The numbers of cases are frequently relatively small. The studies are inevitably cross-sectional and retrospective. We and others have presented data suggesting that the decline in β-cell mass in type 2 diabetes is caused by increased β-cell apoptosis (3,6). Therefore, these data suggest that inhibition of β-cell apoptosis to avoid a β-cell deficit might be effective to delay and/or avoid the onset of diabetes. Indeed, both metformin and thiazolidinediones have been reported to inhibit β-cell apoptosis in vitro (6,7) and to delay onset of type 2 diabetes in clinical studies (8,9). The potential mechanisms underlying increased β-cell apoptosis in type 2 diabetes include toxicity from islet amyloid polypeptide oligomer formation, free fatty acids (lipotoxicity), free oxygen radical toxicity and, once hyperglycemia supervenes, glucose-induced apoptosis (glucotoxicity) (10,11).

The steep increase in blood glucose concentration with β-cell deficiency is consistent with the well-known deleterious effects of hyperglycemia per se on β-cell function. These include defective glucose sensing due to reduced glucokinase activity (12), impaired glucose-induced insulin secretion due to increased uncoupling protein two activity (13), and depletion of immediately secretable insulin stores (14). Also, hyperglycemia reduces insulin sensitivity, further compounding the effects of decreased in-

From the [1]Larry Hillblom Islet Research Center, UCLA David Geffen School of Medicine, Los Angeles, California; and the [2]Division of Endocrinology, Mayo Clinic, Rochester, Minnesota.

Address correspondence and reprint requests to Peter C. Butler, MD, Larry Hillblom Islet Research Center, UCLA David Geffen School of Medicine, 24-130 Warren Hall, 900 Veteran Ave., Los Angeles, CA 90095-7073. E-mail: pbutler@mednet.ucla.edu.

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A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

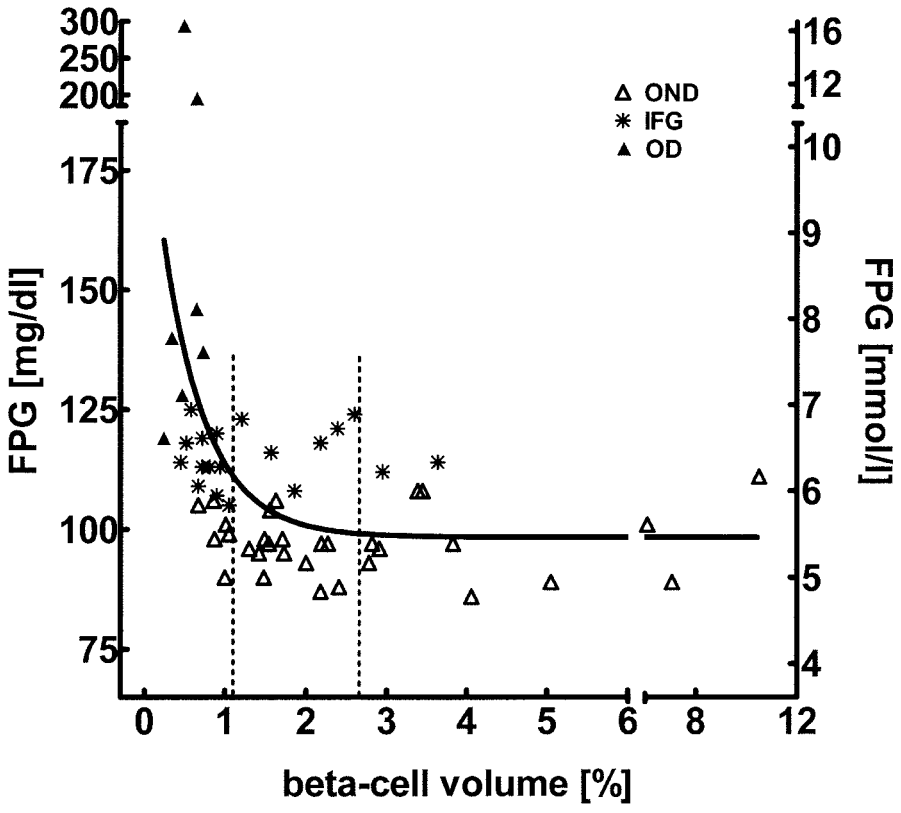

Figure 1—*Relationship between percentage of pancreas volume occupied by β-cells and fasting plasma glucose in obese humans without insulin or oral antidiabetic treatment. The solid line is derived from nonlinear regression analysis (monoexponential fit,* r = *0.50;* P < *0.0001 by ANOVA). The dashed vertical lines indicate the mean β-cell area in obese nondiabetic subjects (OND)* (right) *and the computed inflection point of the curve* (left).

sulin secretion (15). While the present data suggest that relatively small increases in β-cell mass might have useful actions in restoring blood glucose control, it is likely that aggressive normalization of blood glucose concentrations is required to accompany the strategy to increase β-cell mass to overcome the afore mentioned deleterious effects of hyperglycemia as well as glucose-induced β-cell apoptosis.

In conclusion, there is a curvilinear relationship between β-cell mass and fasting blood glucose concentration in humans. These data provide some guidelines for the efforts targeted toward restoring β-cell mass to reverse diabetes, or prevention of diabetes by protection of β-cell mass. The present data describe just one time point. Data regarding movement up or down the currently described curve in humans will only be available if it becomes possible to measure β-cell mass in vivo.

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