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Journal Title: Diabetes Care
Volume: Volume 36, Number 9
Publisher: American Diabetes Association | 2013-09-01, Pages 2772-2778
Type of Work: Article | Final Publisher PDF
Publisher DOI: 10.2337/dc12-2290
Permanent URL: https://pid.emory.edu/ark:/25593/rkm36

Final published version: http://dx.doi.org/10.2337/dc12-2290

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Accessed June 7, 2018 2:59 PM EDT
Evidence of Reduced β-Cell Function in Asian Indians With Mild Dysglycemia

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Objective — To examine β-cell function across a spectrum of glycemia among Asian Indians, a population experiencing type 2 diabetes development at young ages despite low BMI.

Research Design and Methods — One thousand two hundred sixty-four individuals without known diabetes in the Diabetes Community Lifestyle Improvement Program in Chennai, India, had a 75-g oral glucose tolerance test, with glucose and insulin measured at 0, 30, and 120 min. Type 2 diabetes, isolated impaired fasting glucose (iIFG), isolated impaired glucose tolerance (iIGT), combined impaired fasting glucose and impaired glucose tolerance (iIGT), combined impaired fasting glucose and impaired glucose tolerance, and normal glucose tolerance (NGT) were defined by American Diabetes Association guidelines. Measures included insulin resistance and sensitivity (homeostasis model assessment of insulin resistance [HOMA-IR], modified Matsuda Index, 1/fasting insulin) and β-cell function (oral disposition index \( \Delta \text{insulin}_{30-300} \Delta \text{glucose}_{0-30} \times 1/\text{fasting insulin} \)).

Results — Mean age was 44.2 years (SD, 9.3) and BMI 27.4 kg/m² (SD, 3.8); 341 individuals had NGT, 672 had iIFG, IGT, or IFG plus IGT, and 251 had diabetes. Patterns of insulin resistance or sensitivity were similar across glycemic categories. With mild dysglycemia, the absolute differences in age- and sex-adjusted oral disposition index (NGT vs. iIFG, 38%; NGT vs. iIGT, 32%) were greater than the differences in HOMA-IR (NGT vs. iIFG, 25%; NGT vs. iIGT, 23%; each \( P < 0.0001 \)). Compared with NGT and adjusted for age, sex, BMI, waist circumference, and family history, the odds of mild dysglycemia were more significant per SD of oral disposition index (iIFG: odds ratio [OR], 0.36; 95% CI, 0.23–0.55; iIGT: OR, 0.37; 95% CI, 0.24–0.56) than per SD of HOMA-IR (iIFG: OR, 1.69; 95% CI, 1.23–2.33; iIGT: OR, 1.53; 95% CI, 1.11–2.11).

Conclusions — Asian Indians with mild dysglycemia have reduced β-cell function, regardless of age, adiposity, insulin sensitivity, or family history. Strategies in diabetes prevention should minimize loss of β-cell function.

Diabetes Care 36:2772–2778, 2013

Type 2 diabetes mellitus is a global problem, with 80% of all cases worldwide occurring in low- and middle-income countries (1). However, despite the increasing prevalence of type 2 diabetes, the etiology of the disease remains incompletely understood. Previously invoked as the driving feature of diabetes, increased insulin resistance can trigger increased insulin production to maintain normoglycemia and, over time, can strain β-cells to the point at which insulin production is no longer adequate (2–4), i.e., “β-cell exhaustion.” Characteristics associated with insulin resistance, particularly older age, obesity, and physical inactivity, are strong risk factors for diabetes (5).

Yet, poor β-cell function also may have more of a primary role in diabetes development. The inadequate β-cell response to physiologic needs for insulin not only may be an acquired feature (e.g., as a result of insulin resistance) but also, at least in some individuals, may be an inherent feature. β-Cell dysfunction has been detected early in the pathogenesis of the disease (6), with recent cross-sectional and longitudinal studies detecting dysfunction in people with prediabetes or even normoglycemia (7–10). Supported by recent genetic discoveries (11), these studies suggest that some individuals have an underlying susceptibility to poor β-cell function (12) and that β-cell dysfunction may be an early driving metabolic feature of diabetes development.

Most studies of diabetes pathogenesis have been conducted in populations of European descent; however, more people have diabetes in other populations worldwide. Asian Indians, in particular, experience high rates of type 2 diabetes (13) at younger ages and lower BMI values (14) compared with other populations. They have high basal insulin levels (15) that are not entirely explained by obesity or adverse fat distribution (16), which are commonly cited factors related to insulin resistance. Considering these characteristics, Asian Indians may be an ideal population to utilize for developing a better understanding of the relative roles of β-cell function and insulin resistance in the pathogenesis of type 2 diabetes. Previous studies that have examined the etiology of diabetes in Asian Indians have produced conflicting findings. Altered β-cell function has been associated with impaired glucose tolerance (IGT) (17), has not been associated with IGT (18,19), and has been associated with impaired fasting glucose (IFG) but not IGT (20). Furthermore, β-cell function has not always been evaluated rigorously in Asian Indians (i.e., expressed relative to the insulin resistance of each individual) (21). We investigated the associations between the pathophysiologic mechanisms of insulin resistance and β-cell function with glycemic status in a large cohort (n = 1,264) of Asian Indians in Chennai, India.
RESEARCH DESIGN AND METHODS

Study population
Study subjects were individuals in the Diabetes Community Lifestyle Improvement Program, a primary prevention trial in Chennai (formerly Madras) testing the effects of a stepwise model of diabetes prevention, including a culturally tailored and intensive lifestyle intervention plus metformin when needed (22). Community-wide recruitment targeted men and women at large-scale community events, housing or apartment complexes, local businesses, places of worship, and educational institutions, through clinic records at the study site, and through direct referral by health care providers at the clinic. Community-based screening (n = 19,377) included a short survey, anthropometric measurements, and random capillary blood glucose test using a glucose meter (Lifescan; Johnson & Johnson, Milpitas, CA). Screened volunteers who were 20–65 years old with a random capillary blood glucose of ≥6.1 mmol/L (110 mg/dl) and without known type 2 diabetes were eligible for clinic-based screening (Diabetes Community Lifestyle Improvement Program baseline testing), which included a 75-g oral glucose tolerance test (OGTT) performed after an overnight fast.

Individuals who were pregnant, breastfeeding, with a history or evidence of heart disease, or with any other serious illness were excluded from the study. All subjects provided informed consent and participated in clinical-based screening between 2008 and 2011. Among the 1,285 individuals tested in clinic-based screening, 14 participants were excluded for missing glucose or insulin measures of the OGTT at any time point (i.e., 0, 30, or 120 min). An additional seven individuals were excluded for having negative or zero values of the insulinogenic index (IGI), a measure of the early insulin response in the OGTT (23), calculated as the ratio of change in insulin to the change in glucose from 0 to 30 min (i.e., ΔI0–30/ΔG0–30). The final number of participants included in the present analyses was 1,264. The study was approved by the Emory University Institutional Review Board and the Madras Diabetes Research Foundation Ethics Committee.

Study procedures
Diabetes Community Lifestyle Improvement Program baseline testing included the collection of demographic, anthropometric, and glucose tolerance data (22). After fasting overnight for at least 8 h, subjects participated in a standard 75-g oral OGTT (24), with plasma glucose and insulin sampled at 0, 30, and 120 min. Other collected data included demographics, body weight, height, waist circumference, and family history of diabetes (defined as having one or more first-degree relatives with type 2 diabetes). For body weight assessment, subjects were asked to wear light clothing and weight was recorded after shoes and heavy jewelry were removed. Height was measured with a stadiometer to the nearest centimeter with subjects standing upright without shoes. BMI was calculated as mass (kg) divided by height squared (m²).

Waist circumference was measured twice at the smallest horizontal girth between the costal margins and the iliac crests were measured at minimal respiration using a nonelastic measuring tape and averaged. OGTT samples were collected in EDTA, separated, and stored at –80°C. Plasma glucose (hexokinase method) was measured on a Hitachi 912 Autoanalyzer (Hitachi, Mannheim, Germany) using kits supplied by Roche Diagnostics (Mannheim, Germany). Insulin concentrations were estimated using an electrochemiluminescence method (COBAS E 411; Roche Diagnostics, Mannheim, Germany). The intra-assay and interassay coefficients of variation for the biochemical assays ranged between 3.1 and 7.6%. Samples were processed in a laboratory accredited nationally by the National Accreditation Board for Testing and Calibration Laboratories and internationally by the College of American Pathologists.

Key variables
The glycemic status outcomes for this study were defined by the following American Diabetes Association criteria (25): diabetes as fasting plasma glucose ≥7.0 mmol/L (126 mg/dl) or 2-h postload glucose ≥11.1 mmol/L (200 mg/dl), or both; isolated IFG (IGF) as fasting plasma glucose 5.6–6.9 mmol/L (100–125 mg/dl) and 2-h postload glucose 7.8–11.0 mmol/L (140–199 mg/dl); isolated IGT (IGT) as 2-h postload glucose 7.8–11.0 mmol/L (140–199 mg/dl) and fasting plasma glucose <5.6 mmol/L (100 mg/dl); and combined IFG and IGT (IFG plus IGT) as fasting plasma glucose 5.6–6.9 mmol/L (100–125 mg/dl) and 2-h postload glucose 7.8–11.0 mmol/L (140–199 mg/dl). Prediabetes was defined as IGF, IGT, or IFG and IGT. Mild dysglycemia was defined as IGF or IGT.

The primary measure for β-cell function was the oral disposition index, denoted as DIo, calculated as follows as IG1 adjusted for insulin sensitivity: DIo = [(ΔI0–30/ΔG0–30) × 1/([fasting insulin]]) (23). Insulin resistance was estimated using homeostasis model assessment of insulin resistance (HOMA-IR; [fasting insulin × fasting glucose]/22.5) (26). The modified Matsuda Index for whole-body insulin sensitivity was calculated as follows: (10,000/square root of [fasting glucose × fasting insulin] × [mean glucose × mean insulin]), with mean glucose and mean insulin each calculated from values at 0, 30, and 120 min of the OGTT (27,28). Total area under the curve (AUC) for insulin and AUC for glucose were calculated using the trapezoidal rule, and a ratio of the two was created (AUCinsulin/glucose). Secondary measures of β-cell function included the following: [(ΔI0–30/ΔG0–30) × 1/HOMA-IR]; [(ΔI0–30/ΔG0–30) × modified Matsuda Index]; AUCinsulin/glucose × (1/fasting insulin); AUCinsulin/glucose × (1/HOMA-IR); and AUCinsulin/glucose × (modified Matsuda Index). Other covariates included BMI and waist circumference. Categories of overweight/obesity were those defined by the World Health Organization (29) both generically (25.0≤BMI<30.0 kg/m² for overweight; BMI ≥30.0 kg/m² for obesity) and specifically for Asian populations (23.0≤BMI≤27.4 kg/m² for overweight; BMI ≥27.5 kg/m² for obesity). Waist circumference was categorized dichotomously, using waist >90 cm for men and ≥80 cm for women (30), and by tertiles.

Statistical analysis
Analyses were performed using SAS 9.3 (SAS Institute, Cary, NC). ANOVA allowed comparison of DIo across glycemic status categories, including the Tukey test for multiple comparisons. Non-normally distributed variables were log-transformed as required to meet assumptions of regression. A Score test was conducted to evaluate the possible use of ordinal logistic regression; the proportional odds could not be assumed as required (i.e., the null hypothesis that the model was constrained by the proportional odds assumption was rejected [χ² = 98.59; degrees of freedom = 3; P < 0.0001]).
comparison of glycemic status groups. Among all participants, the mean age was 44.2 years (SD, 9.3), and 37% were female. According to specific criteria, 53.2% had prediabetes (15.8% with iIFG; 16.0% with iIGT). Diabetes, 0.51. HOMA-IR, fast-

Results Table 1 provides baseline characteristics for the participants across glycemic status groups. Among all participants, the mean age was 44.2 years (SD, 9.3), and 37% were female. According to specific criteria, 53.2% had prediabetes (15.8% with iIFG; 16.0% with iIGT). Diabetes, 0.51. HOMA-IR, fast-

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Data are mean and SD unless otherwise stated. *Geometric mean and geometric SD provided for DIo and secondary measures of β-cell function.
except iIFG and iIGT. Compared with NGT, HOMA-IR was 25% greater in iIFG and 23% greater in iIGT (both \(P < 0.0001\)). However, unlike HOMA-IR, the modified Matsuda Index was significantly different between every pair-wise comparison of glycemic status groups except between iIFG and IFG plus IGT, iIGT and diabetes, and IFG plus IGT and diabetes. Differences between glycemic status levels remained after adjustment for age and sex (Fig. 1). Furthermore, differences in mean \(D_{\text{Io}}\) persisted after adjustment for age, sex, BMI, waist circumference, and family history as follows: \(D_{\text{Io}}\) was 2.48 L/mmol in NGT vs. 1.55, 1.69, 1.00, and 0.50 L/mmol in iIFG, iIGT, IFG plus IGT, and diabetes, respectively (all \(P < 0.0001\) vs. NGT). Across the same glycemic categories, HOMA-IR (mmol\(_{\text{glu}}\) × pmol\(_{\text{ins}}\)/L\(^2\)) was 15.29, 18.52, 18.02, 21.98, and 28.18 (all \(P < 0.05\) vs. NGT) and the modified Matsuda Index [L\(^2\)/mmol\(_{\text{glu}}\) × pmol\(_{\text{ins}}\)] was 13.31, 11.14, 9.49, 9.55, and 8.09 (all \(P < 0.0001\) vs. NGT), and all were adjusted for age, sex, BMI, waist circumference, and family history.

A hyperbolic relationship was found between insulin sensitivity and insulin secretion. Using linear regression to estimate ln(IGI) as a function of ln(1/fasting insulin), the slope and its 95% CI for each glycemic category did not equal zero and were negative. For example, among individuals with diabetes, the slope of regression was \(-0.8 (95\%\ CI, -0.9 to -0.6)\). Secondary measures of β-cell function also were evaluated for hyperbolic relationships between components. The hyperbolic relationship of IGI and 1/HOMA-IR was poorer than IGI and 1/fasting insulin; among those with diabetes, the slope of regression between IGI and 1/HOMA-IR was \(-0.6 (95\%\ CI, -0.7 to -0.4)\). In contrast, the relationship improved slightly using the modified Matsuda Index instead of 1/fasting insulin (\(-0.9; 95\%\ CI, -1.1 to -0.8)\). The hyperbolic relationships between AUC\(_{\text{ins/glu}}\) and the insulin sensitivity measures were similar to or better than those between IGI and the various insulin sensitivity measures. The weakest relationship with AUC\(_{\text{ins/glu}}\) was found with 1/HOMA-IR.

No interactions were found between \(D_{\text{Io}}\) and sex, age, BMI, or waist circumference. Polytomous logistic regression was used to determine the odds of each hyperglycemic status category compared with NGT for incremental changes in \(D_{\text{Io}}\), HOMA-IR, and other covariates. Regression results are shown in Table 2. \(D_{\text{Io}}\) and HOMA-IR were each independently associated with glycemic status, as shown in model 1. The odds for each glycemic category compared with NGT were significantly lower for every SD increase in \(D_{\text{Io}}\), both in prediabetes and in diabetes (each \(P < 0.0001\)). In particular, the odds ratio (OR) of diabetes compared with NGT was extremely small for each SD increase in \(D_{\text{Io}}\). Almost no change in the magnitude of association between \(D_{\text{Io}}\) and glycemic status was found after adjustment for age, for age, BMI, waist circumference, or for age, BMI, waist circumference, and family history (Table 2, models 2, 3, 4). In contrast to \(D_{\text{Io}}\), the odds for any glycemic category compared with NGT were greater for every SD increase in HOMA-IR. Adjustment for age, BMI, waist circumference, and family history did not substantially change the magnitude of association between HOMA-IR and glycemic status.

Polytomy regression with secondary measures of β-cell function yielded more pronounced findings, with the relative contributions of β-cell function on glycemic status exceeding that of HOMA-IR. For the measure AUC\(_{\text{mats}}\) × modified Matsuda, which exhibited the best hyperbolic relationship between insulin secretion and insulin sensitivity, β-cell function was independently associated with glycemic status (iIFG: OR, 0.11; 95% CI, 0.07–0.16; iIGT: OR, 0.34; 95% CI, 0.25–0.46) and HOMA-IR was not associated with glycemic status (iIFG: OR, 0.94; 95% CI, 0.66–1.33; iIGT: OR, 1.16; 95% CI, 0.84–1.60).

CONCLUSIONS—This study underscores the importance of β-cell dysfunction relative to insulin resistance across glycemic status groups in Asian Indians, particularly iIFG and iIGT. Using an index of β-cell function relative to insulin sensitivity, \(D_{\text{Io}}\), a highly significant difference in \(D_{\text{Io}}\) was observed between NGT and iIFG or iIGT. A difference in insulin resistance, as measured by HOMA-IR, also was observed; however, the difference in mean HOMA-IR was greatest between IFG plus IGT and diabetes, whereas the greatest difference in mean \(D_{\text{Io}}\) was between NGT and iIFG. Results
from statistical modeling showed that the relative contributions of DIo to IFG and to iGt were greater than those of HOMA-IR, even after adjustment for variables known to impact disease development, including age, BMI, waist circumference, and family history of diabetes. These findings suggest that despite conflicting studies (17–20) in Asian Indians, a decrease in β-cell function may be a primary etiological factor in the development of type 2 diabetes in this ethnic group.

DIo was selected as the primary measure of β-cell function for several reasons. First, the measure agrees with the biological constructs known for β-cell function, because secretion of insulin is measured relative to the prevailing levels of insulin sensitivity in the body (21). Second, mathematical confirmation in studies with more rigorous designs has demonstrated a hyperbolic relationship of the two components (i.e., insulin secretion and insulin sensitivity) (23,32). Third, autocollinearity between the components of DIo is unlikely to drive the hyperbolic relationship, as described elsewhere (31). Fourth, longitudinal studies have indicated that DIo is a good measure of disease processes related to β-cell function, because it predicts the development of future diabetes (23). In addition to DIo, alternative measures of β-cell function were analyzed. Like another study, our results suggest that (AUC$_{\text{ins}}$ × modified Matsuda Index) and (AUC$_{\text{ins}}$ × fasting insulin) should be examined further as potentially strong measures of DIo (32). Across measures of β-cell function, similar findings indicated that the relative contribution of β-cell function toward glycemic status categories was greater than that of insulin resistance.

Studies that have examined β-cell function in various ethnic groups (i.e., β-cell function defined as insulin secretion with adjustment for insulin sensitivity within individuals) (12,21) have shown alternative patterns across glycemic phenotypes compared with those found in the current study. In a study of 1,399 normal-weight Japanese adults, those with IFG were found to have somewhat preserved β-cell function using the ratio of change in AUC for plasma insulin to plasma glucose (ΔAUC$_{\text{PG}}$/ΔAUC$_{\text{PG}}$) from 0 to 120 min of the OGTT after adjustment of the Matsuda Index. This measure of the disposition index was reduced in IFG (mean ± SEM, 7.1 ± 0.5; P < 0.05) with IFG defined as fasting plasma glucose 6.1–6.9 mmol/L) after 5 years of follow-up. However, among all individuals with NGT at baseline (n = 3,145), those who would later develop iIFG (NGT to iIFG) had lower mean DIo at baseline compared with those who would eventually develop iGt (NGT to iGt). This study showed that early-phase DIo was significantly higher in those who developed iIFG compared with iIGT. In another study of 1,272 Chinese adults, a decline in early phase DIo ( ΔAUC$_{\text{PG}}$/ΔAUC$_{\text{PG}}$ at 30 min, adjusted with the Matsuda Index) was found in both IFG (fasting glucose 5.6–7.0 mmol/L) and iGt—both significantly lower than NGT—but DIo in iGt also was significantly lower than DIo in IFG (both P < 0.05) (34). The current study showed that early-phase DIo was significantly higher in those who developed iIFG compared with iIGT.
populations in which the progression toward diabetes is particularly rapid, the level of $D_i$ in normoglycemia may be an important factor related to disease risk. Future multiethnic studies are needed to determine if and how $\beta$-cell decline varies by ethnicity and to what degree differences lie between iIFG and iIGT.

This study has several important strengths. It contains a large, well-characterized, community-based sample stemming from the screening of almost 20,000 people and, therefore, was not limited to hospital- or clinic-based samples. All cases of diabetes were newly diagnosed. A hyperbolic relationship was found between insulin sensitivity and insulin secretion using linear regression to estimate $\ln(D_{i0.30}/D_{G0.30})$ as a function of $\ln(1/\text{fasting insulin})$, indicating appropriate use of the disposition index as a measure of $\beta$-cell function. We used standardized regression to enable comparison of variables that were measured in different units and, consequently, to directly compare the relative contributions of $\beta$-cell function and HOMA-IR to the development of prediabetes and diabetes.

The limitations of this study include its cross-sectional design, limiting further inquiry regarding temporality, and the degree of representation of the sample, because results may not be generalizable to other populations (e.g., other racial/ethnic groups). In addition, all subjects had a random blood glucose level of $\geq 6.1 \text{ mmol/L}$ before receiving the OGTT and, therefore, the NGT group may not be representative of normoglycemia. However, if the NGT group had normal random blood glucose levels, even greater differences between NGT and iIFG or iIGT groups would be expected. Therefore, our results provide conservative estimates of the lower $\beta$-cell function and higher insulin resistance in iIFG and iIGT relative to NGT groups. We excluded seven individuals for having negative or zero values of the insulinogenic index, values considered biologically implausible; however, this number comprises a very small percentage of the total sample (0.5%), smaller than reported in another study (2.7%) (23). Only one OGTT test was performed for each participant, and thus the classification of some individuals may have changed if the OGTT had been performed a second time. Another limitation pertains to the use of an OGTT-derived measure of $\beta$-cell function, rather than estimates based on the glucose clamp technique or the frequently sampled intravenous glucose tolerance test as used by Bergman et al. (21), who showed that insulin secretion had a hyperbolic relationship (i.e., $y = \text{constant}/x$) with the existing state of insulin sensitivity. The findings here, using the measure of $D_{i0.30}$ for $\beta$-cell function, are consistent with several other studies that used euglycemic clamps and intravenous glucose tolerance tests. These studies have shown that poor insulin secretion begins sometime during normoglycemia (35, 36). Also, they have highlighted that potential differences in $\beta$-cell dysfunction may exist between IFG and IGT phenotypes (37–39), particularly that impairment of $\beta$-cell function may occur in iIFG at least as much as in iIGT.

Although the disposition index was originally based on intravenous sampling techniques, an OGTT-derived measure has been shown to be valid (23) and may include additional benefits in the study of $\beta$-cell function. The hyperbolic relationship between insulin sensitivity and insulin secretion has been demonstrated using OGTT data, indicating that $D_{i0.30}$ is a valid measure of $\beta$-cell function and is highly predictive of 10-year incidence of diabetes (23). Several metabolic factors, such as glucose disposition, differ between oral and intravenous glucose loads as related to different responses in the liver and in the periphery and, thus, OGTTs may probe important physiological processes in glucose metabolism that cannot be studied through intravenous testing. Finally, OGTTs are easy to perform in populations, making them more convenient for epidemiological studies in which recruitment of sufficiently large study samples can correct for within-subject variability (23, 31, 40). The minimum sample size needed to detect a 20% change when using the insulinogenic index is 181 (40), a number far exceeded by the sample size of the current study. Thus, $D_{i0.30}$ is a valid, informative, and practical approach to the study of $\beta$-cell function.

Using a robust measure of $\beta$-cell function, the current study provides evidence that those in any category of dysglycemia, including iIFG and iIGT, have lower $\beta$-cell function compared with those in the NGT category. This study also showed that insulin resistance was greater across all categories of dysglycemia compared with NGT. However, the relative contribution of insulin resistance was not as great as that of $\beta$-cell function in any given glycemic status group. As such, the primary prevention and control of diabetes will require strategies to preserve $\beta$-cell function and reduce $\beta$-cell decline.

In conclusion, our data demonstrate markedly reduced $\beta$-cell function among Asian Indians with mild dysglycemia. These abnormalities cannot be attributed to differences in age, adiposity, insulin sensitivity, or family history. Prospective studies are needed to further investigate the relative roles of $\beta$-cell dysfunction and insulin resistance in the early natural history of diabetes.

Acknowledgments—The project is supported by a BRIDGES grant from the International Diabetes Federation. BRIDGES, an International Diabetes Federation project, is supported by an educational grant from Lilly Diabetes. This project also was supported by Emory Global Health Institute, Molecules to Humankind Program sponsored by the Burroughs Wellcome Fund (L.R.S.), the National Institutes of Health T32 grant (5T32DK007298-33 to M.B.W.), VA award HSR&D IIR 07-138 (L.S.P. and K.M.V.N.), and Cystic Fibrosis Foundation award PHILLI12A0 (L.S.P.).

No potential conflicts of interest relevant to this article were reported.

L.R.S. analyzed data, wrote the manuscript, drafted tables and figures, and reviewed and revised the manuscript. M.B.W. and H.R. researched data and reviewed and revised the manuscript. M.K.A. and J.B.E.-T. reviewed and revised the manuscript. L.S.P. contributed to analysis, discussion, and reviewed and revised the manuscript. K.M.V.N. contributed to concept, design, and analysis and reviewed and revised the manuscript. L.R.S. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

This is the 8th paper from Global Diabetes Research Centre (GDRC)—a collaboration between Madras Diabetes Research Foundation, Chennai, India, and Emory University, Atlanta, Georgia (GDRC-8). Parts of this study were presented at the 71st Scientific Sessions of the American Diabetes Association, San Diego, California, 24–28 June 2011.

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Reduced β-cell function and dysglycemia

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