Prediction of Diabetes Based on Baseline Metabolic Characteristics in Individuals at High Risk

OBJECTIVE—Individuals with impaired glucose tolerance (IGT) are at high risk for developing type 2 diabetes mellitus (T2DM). We examined which characteristics at baseline predicted the development of T2DM versus maintenance of IGT or conversion to normal glucose tolerance.

RESEARCH DESIGN AND METHODS—We studied 228 subjects at high risk with IGT who received treatment with placebo in ACT NOW and who underwent baseline anthropometric measures and oral glucose tolerance test (OGTT) at baseline and after a mean follow-up of 2.4 years.

RESULTS—In a univariate analysis, 45 of 228 (19.7%) IGT individuals developed diabetes. After adjusting for age, sex, and center, increased fasting plasma glucose, 2-h plasma glucose, ΔG0–120 during OGTT, HbA1c, adipocyte insulin resistance index, ln fasting plasma insulin, and ln ΔG0–3 during OGTT were associated with increased risk of diabetes. At baseline, higher insulin secretion (ln [ΔG0–120/ΔG0–120]) during the OGTT was associated with decreased risk of diabetes. Higher β-cell function (insulin secretion/insulin resistance or disposition index; ln [ΔG0–120/ΔG0–120 × Matsuda index of insulin sensitivity]; odds ratio 0.11; P < 0.0001) was the variable most closely associated with reduced risk of diabetes.

CONCLUSIONS—In a stepwise multiple-variable analysis, only HbA1c and β-cell function (ln insulin secretion/insulin resistance index) predicted the development of diabetes (r = 0.49; P < 0.0001).

Diabetes Care 36:3607–3612, 2013

In individuals with impaired glucose tolerance (IGT) are at high risk for diabetes; ~50% of all IGT subjects progress to diabetes during their lifetime, with annual diabetes conversion rates that vary between 3 and 11% (1,2). Therefore, it is important to identify these individuals at high risk and to institute preventive therapy, be it lifestyle modification (3,4) or pharmacologic therapy, to prevent the development of microvascular and macrovascular complications (5–11).

In ACT NOW, 602 IGT subjects at high risk were randomly assigned to receive therapy with placebo or pioglitazone, in addition to advice about diet and exercise (7,12). During a mean follow-up period of 2.4 years, subjects in the placebo and pioglitazone groups experienced conversion to diabetes at the rates of 7.6 and 2.1%, respectively (hazard ratio 0.28; P < 0.00001). All subjects in ACT NOW underwent baseline phenotype, anthropometric, and clinical measurements. An oral glucose tolerance test (OGTT) measuring plasma glucose, free fatty acid (FFA), insulin, and C-peptide (CP) concentrations was performed to provide indices of glucose tolerance, insulin secretion, β-cell function, and insulin sensitivity at baseline (12–17). In the current study, we describe those variables that are independent predictors of type 2 diabetes mellitus (T2DM) in IGT subjects treated with placebo in ACT NOW, and we describe a multivariate model that is highly predictive of the eventual development of diabetes. In the predictive model, we used variables that are routinely obtained by practicing physicians, as well as physiologic variables derived from the OGTT.

RESEARCH DESIGN AND METHODS

Subjects
A total of 602 subjects at high risk (fasting plasma glucose [FPG] of 95–125 mg/dL and at least one additional risk factor for diabetes) with IGT (2-h plasma glucose 140–199 mg/dL) comprised the ACT NOW study population. Additional inclusion and exclusion criteria have been published (7,12). Demographic, anthropometric, and metabolic characteristics of the 602 subjects at baseline were similar in pioglitazone-treated and placebo-treated groups and have been published previously (7). In this study, we report 228 placebo-treated IGT subjects who completed the study and underwent an end-of-study OGTT or who experienced...
conversion to diabetes and underwent an end-of-study OGTT (Table 1). Subjects who were treated with pioglitazone, lost to follow-up, or who dropped out and did not undergo end-of-study OGTT were not included in the present analysis.

**Study design**
Detailed descriptions of the study design (12) and results have been published (1). Briefly, eight centers participated in the study, which was approved by each site's Institutional Review Board. After eligibility was determined, 602 IGT subjects were randomized by center or sex to receive pioglitazone or placebo. Subjects were followed up until they reached the primary end point of diabetes, dropped out, were lost to follow-up, or reached study end. FPG was determined at each follow-up visit. HbA1c was measured every 6 months, and FFA concentrations were measured at a Gulick II Tape Measure (Gays Mills, WI) at the midpoint between the highest point at the iliac crest and the lowest part of the costal margin in the midaxillary line. Total body fat and percent body fat were measured by dual-energy X-ray absorptiometry (Hologic 4500; Hologic, Boston, MA).

Participants were randomized to pioglitazone 30 mg/day or placebo and returned at 2, 4, 6, 8, 10, and 12 months during the first year and then every 3 months thereafter. Subjects were followed-up until they reached the primary end point of diabetes, dropped out, were lost to follow-up, or reached study end. FPG was determined at each follow-up visit. HbA1c was measured every 6 months, and OGTT was performed annually. Baseline measurements were repeated at the end of the study or at the time of conversion to diabetes.

**IGT conversion to diabetes.** The primary outcome was development of diabetes defined as FPG ≥126 mg/dL or 2-h glucose during OGTT ≥200 mg/dL. The diagnosis was confirmed by a repeat OGTT (2-h glucose ≥200 or FPG ≥126 mg/dL).

**Data analysis**
Matsuda index (MI) of insulin sensitivity was calculated from plasma glucose and insulin concentrations during OGTT (18) as follows:

$$MI = \frac{10,000}{(FPI \times FPG) \times MPI \times MPG}$$

MPI and MPG indicate mean plasma insulin and mean plasma glucose concentrations, respectively, during the OGTT.

The incremental area under plasma glucose, insulin, CP, and FFA curves during OGTT were determined using the trapezoidal rule. Insulin secretion rate (ISR) was calculated from deconvolution of the plasma CP concentration curve (19). \(\Delta I, \Delta ISR, \Delta I/\Delta G, \text{and } \Delta ISR/\Delta G\) were calculated as indices of insulin secretion during the OGTT, where \(\Delta = \) increment above baseline. The \(\beta\)-cell function during the OGTT was calculated as the insulin secretion/insulin resistance (disposition) index using the following three different estimates of insulin secretion: \(\Delta I_{0-120}/\Delta G_{0-120} \times MI, \Delta CP_{0-120}/\Delta G_{0-120} \times MI, \text{and } \Delta ISR_{0-120}/\Delta G_{0-120} \times MI\), where \(0-120\) represents the 0- to 120-min time point during the OGTT (3-6). The MI was calculated as described previously (18). The early insulin response was calculated as \(\Delta I_{0-30}/\Delta G_{0-30} \times MI, \Delta CP_{0-30}/\Delta G_{0-30} \times MI, \text{and } \Delta ISR_{0-30}/\Delta G_{0-30} \times MI\). The adipocyte insulin resistance index was calculated as the product of fasting plasma insulin and FFA concentrations (20).

Metabolic syndrome was defined according to the American Heart Association and the Updated National Cholesterol Education Program Adult Treatment Program III definition (21) (i.e., three criteria among the following: increased waist circumference (men, >40 inches or 102 cm; women, >35 inches or 88 cm), elevated triglycerides ≥150 mg/dL (1.7 mmol/L), reduced HDL cholesterol (men, <40 mg/dL or 1.03 mmol/L; women, <50 mg/dL or 1.29 mmol/L), elevated blood pressure ≥130/85 mmHg.

### Table 1—Baseline characteristics of the 228 placebo-treated IGT subjects who underwent baseline and end-of-study OGTTs

| Characteristic                  | Placebo (n = 228) |
|--------------------------------|-------------------|
| Isolated IGT (n)               | 73                |
| IGT/IFG (n)                    | 155               |
| Female/male ratio (%)          | 98:42             |
| Race or ethnic group (n)       |                   |
| Hispanic                       | 54                |
| White                          | 137               |
| Black                          | 30                |
| Other                          | 7                 |
| Family history of diabetes [n (%)] | 126 (55)         |
| Mean age (years)               | 52.5 ± 0.8        |
| Mean BMI (kg/m²)               | 34.4 ± 0.4        |
| Waist circumference (cm)       |                   |
| Men                            | 112 ± 1           |
| Women                          | 103 ± 1           |
| HbA1c (%)                      | 5.60 ± 0.03       |
| FPG (mg/dL)                    | 103 ± 0.5         |
| 2-h plasma glucose (mg/dL)     | 169 ± 1           |
| Fasting plasma insulin (mU/L)  | 10.2 ± 0.6        |
| Lipid levels (mg/dL)           |                   |
| Total cholesterol              | 171 ± 2           |
| LDL cholesterol                | 106 ± 2           |
| HDL cholesterol                | 41 ± 1            |
| Triglycerides                  | 118 ± 4           |
| Fasting FFAs (µmol/L)          | 547 ± 13          |
| Blood pressure (mmHg)          |                   |
| Systolic                       | 127 ± 1           |
| Diastolic                      | 73 ± 1            |

Data are mean ± SD unless otherwise indicated.
or use of medication for hypertension, or elevated fasting glucose ≥100 mg/dL [5.6 mmol/L] or use of medication for hyperglycemia).

Statistical analysis addressed what metabolic, physiologic, anthropometric, or clinical parameters at baseline predict the development of T2DM in IGT subjects treated with placebo and followed up for a mean of 2.4 years. Intention-to-treat analyses were conducted using all available data for the period of follow-up. Baseline insulin concentration, insulin area under the curve, MI of insulin sensitivity, adipose tissue insulin resistance index, and insulin secretion/insulin resistance index were In-transformed before analysis. Normality of distribution was tested by the Kolmogorov-Smirnov test. After adjusting for age, sex, and center, we examined the independent factors that predicted the development of diabetes in IGT subjects treated with placebo. We then used stepwise regression analysis including all variables that could be routinely measured in a physician’s office (FPG, Hba1c, blood pressure, family history of diabetes, BMI, waist circumference, and plasma lipid profile). In a second analysis, we used those variables from the previous stepwise regression analysis that were associated with development of diabetes and also added all OGTT-derived variables.

Methods for determination of Hba1c and plasma glucose, insulin, CP, and lipids were published previously (7). All statistical tests were two-sided. Statistical significance was accepted for α < 0.05. Data are presented as the mean ± SE or median (Table 1 and Fig. 1).

RESULTS

Study cohort
The study population (n = 228; 58% female) had a mean age of 52.5 ± 0.8 years and mean BMI of 34.4 ± 4.0 kg/m²; 155 subjects had both IGT and impaired fasting glucose (IFG), and 73 had isolated IGT (Table 1). Baseline Hba1c, FPG, and 2-h plasma glucose were 5.60 ± 0.03%, 105 ± 0.5 mg/dL, and 169 ± 1 mg/dL, respectively.

Follow-up results
During a median follow-up of 2.4 years, 45 of 228 (19.7%) individuals in the placebo-treated IGT group developed diabetes. The annual average incidence rate of diabetes, calculated using person-years, was 8.2%.

Prediction of diabetes from baseline characteristics
After adjusting for age, sex, and center, increased FPG (odds ratio [OR] 1.11; P < 0.0001), 2-h plasma glucose (1.03; P < 0.0001), ΔG0-120 (1.01; P = 0.001), and Hba1c (8.37; P < 0.0001) at baseline and a positive family history (first-degree relative) of diabetes (2.46; P = 0.02) were associated with increased risk of diabetes. Higher adipocyte insulin resistance (1.48; P = 0.03), ln fasting plasma insulin (1.56; P = 0.07), and ln ΔI0-120 (0.61; P = 0.08) were or tended to be associated with increased risk for diabetes. At baseline, higher insulin secretion (ln ΔI0-120/ΔG0-120; OR 0.44; P = 0.003) and higher ln ΔISR0-120/ΔG0-120 (0.25; P = 0.003) were associated with decreased risk of diabetes. Higher B-cell function (insulin secretion/insulin resistance or disposition index = ln [ΔI0-120/ΔG0-120 × MI]; OR 0.11; P < 0.0001) at baseline was the variable most closely associated with reduced risk of diabetes.

At baseline, reduced insulin sensitivity (MI) (OR 0.92; P = 0.22), higher BMI (1.02; P = 0.40), higher percent body fat (1.02; P = 0.40), and higher waist circumference (0.99; P = 0.37) were not significantly related to future diabetes risk. Increased total cholesterol (1.02; P < 0.05) and reduced HDL (1.05; P = 0.01) at baseline were associated with increased risk for diabetes, whereas plasma triglycerides (1.01; P = 0.78), LDL cholesterol (0.99; P = 0.15), triglyceride/HDL cholesterol ratio (1.13; P = 0.14), and blood pressure (systolic blood pressure: OR 1.00; P = 0.85; diastolic blood pressure: OR 1.01; P = 0.60) were not associated with increased risk of T2DM.

At baseline, 63% of the subjects had the metabolic syndrome (defined according to the American Heart Association and the Updated National Cholesterol Education Program Adult Treatment Program III criteria). Metabolic syndrome was associated with increased risk of development of diabetes (OR 2.8; P = 0.009).

Relationship between plasma insulin response to hyperglycemia and insulin sensitivity
At baseline, the plot of insulin sensitivity (MI) versus the plasma insulin response to hyperglycemia (ΔI0-120/ΔG0-120) during the OGTT was curvilinear. It became linear on In transformation (Fig. 1).

Predictive model
Using the cohort of 228 IGT subjects who received placebo treatment in the ACT NOW study, we performed a multivariable stepwise regression analysis to examine which factors (that routinely could be measured in the physician’s office) at baseline were associated with end-of-study glucose tolerance status (normal glucose tolerance [NGT] and IGT compared with T2DM). In this analysis, only Hba1c, FPG, and family history of diabetes predicted the development of T2DM (r = 0.45; P < 0.0001). Of these three variables (after adjusting for age, sex, and center), Hba1c had the greatest predictive power for future glucose tolerance status (R² = 0.124; P < 0.0001). Sequential addition of the FPG (adjusted R² = 0.164; P < 0.0001) and family history of diabetes (adjusted R² = 0.178; P < 0.0001) provided only a modest further increase. Individuals with Hba1c of 5.6–5.9% (n = 69) and Hba1c of 6.0–6.4% (n = 20) were at increased risk (OR 2.5 [P = 0.01] and OR 12.4 [P < 0.0001], respectively) for developing diabetes compared with those with Hba1c < 5.5% (n = 139). Subjects with combined IGT and IFG (n = 155) at baseline were at increased risk (OR 3.0; P = 0.008) for developing diabetes compared with individuals with isolated IGT. When OGTT-derived physiologic variables were included with Hba1c, FPG, and family history of diabetes in a stepwise multivariable regression analysis, only Hba1c and In insulin secretion/insulin resistance were included in the model.

Figure 1—Relationship between the MI of insulin sensitivity and insulin secretion (ΔI0-120/ΔG0-120) before (A) and after In transformation (B).

DeFronzo and Associates

care.diabetesjournals.org
resistance predicted the development of diabetes \( (r = 0.49; P < 0.0001) \).

Of the easiest measured metabolic and physiologic parameters, HbA1c had the greatest predictive value (adjusted \( R^2 = 0.124; P < 0.0001 \)). Addition of the 2-h plasma glucose (adjusted \( R^2 = 0.143; P < 0.0001 \)) or \( \Delta_{120} \) (adjusted \( R^2 = 0.142; P < 0.0001 \)) during the OGTT increased the prediction of diabetes development only modestly. Addition of \( \Delta_{120} \) (adjusted \( R^2 = 0.157; P < 0.0001 \)) or \( \Delta_{120}/\Delta_{G_{120}} \) (adjusted \( R^2 = 0.157; P < 0.0001 \)) to HbA1c modestly increased the prediction of diabetes more than the addition of \( \Delta_{G_{120}} \) to HbA1c did.

**CONCLUSIONS**—The prevalence of T2DM has increased to epidemic proportions in the United States and throughout the world (22), and this epidemic has been driven by the epidemic of obesity (23). T2DM and its associated microvascular and macrovascular complications cause considerable morbidity and mortality and represent a major burden on the health care economy (24). Therefore, in individuals at high risk, it is reasonable to consider interventions that will reduce the incidence of T2DM and its associated complications. Subjects with IGT are at high risk for development of T2DM (1), and individuals with combined IGT and IFG are at especially high risk (25,26), as substantiated by the present findings. Thiazolidinediones improve insulin secretion (17) and enhance insulin sensitivity (27–30); therefore, they represent a logical choice for treatment of individuals with IGT and IFG (5–8,31–34). In ACT NOW (7), we previously reported that pioglitazone decreased the conversion rate of IGT to T2DM by 72%, and 42% of pioglitazone-treated subjects reverted to NGT. In this study, we examined the physiologic, metabolic, and anthropometric parameters measured at baseline that predict final glucose tolerance status in ACT NOW participants treated with placebo. Indices of glycemic control (increased FPG, glucose area under the curve \( G_{120} \), and HbA1c), increased fasting plasma insulin, higher insulin secretion, low insulin secretion or insulin resistance index, family history of diabetes, and presence of the metabolic syndrome were associated with the development of T2DM in subjects treated with placebo. IGT subjects with the best \( \beta \)-cell function at baseline were least likely to develop diabetes in the placebo-treated group. These observations are consistent with results of a prospective study in which Hispanic women at high risk with history of gestational diabetes mellitus were followed up for 3.8 years (33). In the current study, low baseline insulin sensitivity, measured with the MI, was not predictive of future development of T2DM. This finding may appear to be somewhat discordant from that reported for women with gestational diabetes mellitus (31), but it should be noted that the majority of IGT subjects in the current study were moderately to severely insulin-resistant, and the narrow range of insulin resistance may have limited our ability to detect a significant relationship. At baseline, no anthropometric parameters predicted the future development of diabetes or reversion to NGT. Again, this most likely is explained by the very high BMI, waist circumference, and percent body fat with little variation among subjects. Although metabolic syndrome, increased total cholesterol, and reduced HDL cholesterol were independent predictors of the development of diabetes, they contributed no additional predictive power beyond that provided by HbA1c. Blood pressure, plasma triglyceride, and LDL cholesterol were not associated with the development of diabetes in IGT individuals.

Multiple studies have documented that individuals with IGT are at high risk for future development of T2DM (1,2). The present results clearly demonstrate that IGT subjects at highest risk for development of diabetes later in life can be identified by their level of \( \beta \)-cell function, as quantitated by the ln insulin secretion/insulin resistance index. Although performance of the OGTT has decreased with the introduction of new diagnostic criteria for diabetes and prediabetes based on the FPG concentration and HbA1c (34), neither FPG nor HbA1c can provide information about \( \beta \)-cell function, which we demonstrate in the current study is the strongest predictor of future diabetes development in subjects with IGT. By performing the OGTT with measurement of plasma insulin concentrations, the physician can derive quantitative information about \( \beta \)-cell function that, when combined with an index of glycemic control (HbA1c), can help to identify IGT individuals at especially high risk for development of T2DM later in life. As a screening tool to identify individuals at high risk who should be selected to undergo an OGTT, the HbA1c, FPG, and family history of diabetes (i.e., variables that are readily available to the physician) can be used to select individuals for performance of the OGTT with measurement of the plasma insulin concentration. Not surprisingly, IGT subjects with HbA1c >6.0% were at increased risk (OR 12.4) for developing diabetes compared with those with HbA1c <5.5%. These individuals at high risk can be targeted for intensive lifestyle management, with or without pharmacologic therapy (35).

Although insulin resistance is a core pathophysiologic abnormality in the progression from NGT to IGT to T2DM (36), overt diabetes does not occur in the absence of \( \beta \)-cell failure (13–16,33). Therefore, it is not surprising that the insulin secretion/insulin resistance (disposition) index at baseline is the strongest predictor of future development of diabetes. However, this measure of \( \beta \)-cell function requires performance of the OGTT with determination of the plasma insulin and glucose concentrations. This requires patient time and adds cost. The OGTT also has some inherent variability. By using HbA1c as a screening tool, individuals at high risk can be selected to undergo the OGTT. HbA1c, in combination with the insulin secretion/insulin resistance index and 1-h plasma glucose during the OGTT (25,26), can be used to select the individuals at highest risk with IGT for pharmacologic intervention.

**Acknowledgments**—This work was supported by Takeda Pharmaceuticals, by grants from the General Clinical Research Center (GCRC) at the University of Tennessee Health Science Center (MO1-RR-00221) and the GCRC at the University of Southern California Keck School of Medicine (MO1-RR-0043), and by the Veterans Affairs institutions in San Antonio (Texas), Phoenix (Arizona), and San Diego (California), which contributed resources and the use of their facilities.

R.A.D. received grants from Amylin and Takeda, serves on the advisory board for Amylin, Takeda, Bristol-Myers Squibb, Novo Nordisk, Janssen, and Boehringer Ingelheim, and is a member of the speaker’s bureau for Novo Nordisk. D.T. received consultant fees from Health Diagnostic Laboratory, Inc. D.C.S. received a Takeda grant to fund the Phoenix Data Coordinating Center. M.B. received consulting fees from Sanofi, Merck, Roche, and Boehringer Ingelheim, received grants from Takeda and Merck, and received fees for participation in review activities from Novartis and Bristol-Myers Squibb. T.A.B. received grant support from Allergan and
Takeda, is a member of the advisory panel and speaker’s bureau for Takeda, and received stock options from Tethys Bioscience. S.C.C. is a full-time employee of Merck. R.R.H. received grant support from AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Sanofi, and Medtronic, is a consultant to Boehringer Ingelheim, Gilead, Intarcia, Isis, Eli Lilly, Novo Nordisk, Roche, and Medtronic, and is a member of the advisory board for Amgen, AstraZeneca, Bristol-Myers Squibb, Gilead, Intarcia, Johnson & Johnson/Janssen, Eli Lilly, Merck, Novo Nordisk, Roche, Sanofi, Daichi Sankyo, and Eli Lilly. S.M. is a speaker for Takeda. R.E.R. received research support from Takeda P.D.R. received research grants from Bristol-Myers Squibb and Novo Nordisk, received speaker support from Amylin, and is a consultant for Bristol-Myers Squibb. A.G. received grant support from AstraZeneca, Gilead, and received stock options from Tethys Bioscience. S.C.C. is a full-time employee of Merck. R.R.H. received grant support from Amylin and Roche and is a consultant for Roche. No other potential conflicts of interest relevant to this article were reported.

R.A.D. and A.G. performed data analysis and wrote the initial draft of the manuscript. D.T., D.C.S., M.B., G.A.B., T.A.B., S.C.C., R.R.H., A.E.K., S.M., R.E.R., F.B.S., N.M., and P.D.R. reviewed the manuscript. R.A.D. 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.

The authors thank the nurses and other technical staff for expert help and the 602 patients who participated in this study.

References
1. Gerstein HC, Santaguida P, Raina P, et al. Annual incidence and relative risk of diabetes in people with various categories of dysglycemia: a systematic overview and meta-analysis of prospective studies. Diabetes Res Clin Pract 2007;78:305–312
2. Edelstein SL, Knowler WC, Bain RP, et al. Predictors of progression from impaired glucose tolerance to NIDDM: an analysis of six prospective studies. Diabetes 1997;46:701–710
3. Knowler WC, Barrett-Connor E, Fowler SE, et al.; Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002;346:393–403
4. Tuomilehto J, Lindström J, Eriksson JG, et al.; Finnish Diabetes Prevention Study Group. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. N Engl J Med 2001;344:1343–1350
5. Knowler WC, Hamman RF, Edelstein SL, et al.; Diabetes Prevention Program Research Group. Prevention of type 2 diabetes with troglitazone in the Diabetes Prevention Program. Diabetes 2003;52:1150–1156
6. Xiang AH, Peters RK, Kjos SL, et al. Effect of pioglitazone on pancreatic beta-cell function and diabetes risk in Hispanic women with prior gestational diabetes. Diabetes 2006;55:517–522
7. DeFronzo RA, Tripathy D, Schwenke DC, et al.; ACT NOW Study. Pioglitazone for diabetes prevention in impaired glucose tolerance. N Engl J Med 2011;364:1104–1115
8. Gerstein HC, Yusuf S, Bosch J, et al.; DREAM (Diabetes REduction Assessment with ramipril and rosiglitazone Medica- tion) Trial Investigators. Effect of rosigli- tzonaz on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial. Lancet 2006;368:1096–1105
9. Zinman B, Harris SB, Neuman J, et al. Low-dose combination therapy with rosiglitazone and metformin to prevent type 2 diabetes mellitus (CANOE trial): a double-blind randomised controlled study. Lancet 2010;376:103–111
10. Chiasson JL, Josse RG, Gomis R, Hanesfeld M, Karasik A, Laakso M; STOP-NIDDM Trial Research Group. Acarbose for prevention of type 2 diabetes mellitus: the STOP-NIDDM randomised controlled trial. Lancet 2002;359:2072–2077
11. Kawamori R, Tajima N, Iwamoto Y, Kashihwagi A, Shimamoto K, Kaku K; Voglibose Ph-3 Study Group. Voglibose for prevention of type 2 diabetes mellitus: a randomised, double-blind trial in Japanese individuals with impaired glucose tolerance. Lancet 2009;373:1607–1614
12. DeFronzo RA, Barnerj M, Bray GA, et al. Actos Now for the prevention of diabetes (ACT NOW) study. BMC Endocr Disord 2009;9:17
13. Gastaldelli A, Ferrannini E, Miyazaki Y, Matsuda M, DeFronzo RA; San Antonio metabolism study. Beta-cell dysfunction and glucose intolerance: results from the San Antonio metabolism (SAM) study. Diabetologia 2004;47:31–39
14. Ferrannini E, Gastaldelli A, Miyazaki Y, Matsuda M, Mari A; DeFronzo RA. Beta-cell function in subjects spanning the range from normal glucose tolerance to overt diabetes: a new analysis. J Clin Endocrinol Metab 2005;90:493–500
15. Abdul-Ghani MA, Jenkinson CP, DeFronzo RA. Insulin secretion and action in subjects with impaired fasting glucose and impaired glucose tolerance: results from the Veterans Administration Genetic Epi- demiology Study. Diabetes 2006;55:1430–1435
16. Abdul-Ghani MA, Tripathy D, DeFronzo RA. Contributions of beta-cell dysfunction and insulin resistance to the pathogenesis of impaired glucose tolerance and impaired fasting glucose. Diabetes Care 2006;29:1130–1139
17. Gastaldelli A, Ferrannini E, Miyazaki Y, Matsuda M, Mari A, DeFronzo RA. Thiazolidinediones improve beta-cell function in type 2 diabetic patients. Am J Physiol Endocrinol Metab 2007;292:E871–E883
18. Matsuda M, DeFronzo RA. Insulin sensitivity indices obtained from oral glucose tolerance testing: comparison with the euglycemic insulin clamp. Diabetes Care 1999;22:1462–1470
19. Van Cauter E, Mestrez F, Sturis J, Polonsky KS. Estimation of insulin secretion rates from C-peptide levels. Comparison of individual and standard kinetic parameters for C-peptide clearance. Diabetes 1992;41:368–377
20. Abdul-Ghani MA, Molina-Carrión M, Jani R, Jenkinson C, DeFronzo RA. Adipocytokines in subjects with impaired fasting glucose and impaired glucose tolerance are resistant to the anti-lipolytic effect of insulin. Acta Diabetol 2008;45:147–150
21. Grundy SM, Cleeman JI, Daniels SR, et al.; American Heart Association; National Heart, Lung, and Blood Institute. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Circulation 2005;112:2733–2752
22. Cowie CC, Rust KF, Byrd-Holt DD, et al. Prevalence of diabetes and impaired fasting glucose in adults in the U.S. popu- lation: National Health And Nutrition Examination Survey 1999-2002. Diabetes Care 2006;29:1263–1268
23. Flegal KM, Carroll MD, Kit BK, Ogden CL. Prevalence of obesity and trends in the distribution of body mass index among US adults, 1999-2010. JAMA 2012;307:491–497
24. Centers for Disease Control and Pre- vention. 2011. National Diabetes Fact Sheet [Internet]. Available from www.cdc. gov/diabetes/pubs/pdf/dnls11.pdf. Accessed 6 August 2013
25. Abdul-Ghani MA, Williams K, DeFronzo R, Stern M. Risk of progression to type 2 diabetes based on relationship between postload plasma glucose and fasting plasma glyc- eose. Diabetes Care 2006;29:1613–1618
26. Abdul-Ghani MA, Lyssenko V, Tuomi T, DeFronzo RA, Group L. Fasting versus postload plasma glucose concentration and the risk for future type 2 diabetes: results from the Botnia Study. Diabetes Care 2009;32:281–286
27. Bays H, Mandarino L, DeFronzo RA. Role of the adipocyte, free fatty acids, and ec- topic fat in pathogenesis of type 2 diabetes mellitus: peroxisomal proliferator-activated receptor agonists provide a rational thera- peutic approach. J Clin Endocrinol Metab 2004;89:463–478
28. Yki-Järvinen H. Thiazolidinediones. N Engl J Med 2004;351:1106–1118
29. DeFronzo RA. Insulin resistance, lipotoxic- ity, type 2 diabetes and atherosclerosis: the missing links. The Claude Bernard Lecture 2009. Diabetesologia 2010;53:1270–1287
30. Spiegelman BM. PPAR-gamma: adipogenic regulator and thiazolidinedione receptor. Diabetes 1998;47:507–514
31. Buchanan TA, Xiang AH, Peters RK, et al. Preservation of pancreatic beta-cell function and prevention of type 2 diabetes by pharmacological treatment of insulin resistance in high-risk Hispanic women. Diabetes 2002;51:2796–2803
32. Xiang AH, Peters RK, Kjos SL, et al. Pharmacological treatment of insulin resistance at two different stages in the evolution of type 2 diabetes: impact on glucose tolerance and beta-cell function. J Clin Endocrinol Metab 2004;89:2846–2851
33. Xiang AH, Wang C, Peters RK, Trigo E, Kjos SL, Buchanan TA. Coordinate changes in plasma glucose and pancreatic beta-cell function in Latino women at high risk for type 2 diabetes. Diabetes 2006;55:1074–1079
34. American Diabetes Association. Standards of medical care in diabetes—2010. Diabetes Care 2010;33(Suppl. 1):S11–S61
35. Nathan DM, Davidson MB, DeFronzo RA, et al.; American Diabetes Association. Impaired fasting glucose and impaired glucose tolerance: implications for care. Diabetes Care 2007;30:753–759
36. DeFronzo RA. Banting Lecture. From the triumvirate to the ominous octet: a new paradigm for the treatment of type 2 diabetes mellitus. Diabetes 2009;58:773–795