DIABETES TECHNOLOGY & THERAPEUTICS
Volume 14, Number 6, 2012

DOI: 10.1089/dia.2011.0245

DTT
Diabetes Technology & Therapeutics

ORIGINAL ARTICLE

Impact of Family History of Diabetes on β-Cell Function and Insulin Resistance Among Chinese with Normal Glucose Tolerance

Gang Chen, M.D.,[1*] Meizhi Li, M.D.,[1*] Yuan Xu, M.D.,[1*] Nianhui Chen, M.D.,[1*] Huibin Huang, M.D.,[1] Jixing Liang, M.D.,[1] Liantao Li, M.D.,[1] Junping Wen, M.D.,[1–3] Lixiang Lin, M.D.,[1] and Jin Yao, M.D.[1]

Abstract

Objective: This study investigated the impact of family history of diabetes (FHD) on β-cell function among Chinese with normal glucose tolerance.

Research Design and Methods: A multistage, stratified, cluster random sampling method was used to select a provincially representative sample from Fujian Province. Eventually, a total of 1,183 subjects were entered into the analysis. Several indexes were used to assess the function of β cells, including homeostasis model assessment (HOMA) of insulin resistance (IR), HOMA of β cells, insulinogenic index (IGI), and disposition index.

Results: Overweight, increased body mass index, higher low-density lipoprotein cholesterol, and higher total cholesterol (TC) were the dominant features of positive FHD (FHD^+). The FHD^+ subjects had lower insulin sensitivity ($P < 0.05$). FHD^+ subjects showed higher risk of IR after adjusting for other risk factors (odds ratio 1.523 [1.272–2.009]). However, there was no significant difference in insulin secretion between the two groups. With the use of the multiple linear regression model, waist circumference (WC) and triglycerides (TGs) were found to be independent risk factors of the decline of insulin sensitivity in FHD^+ subjects, and insulin sensitivity declined significantly ($P < 0.05$) with the increase of WC and TGs. In addition, the offspring of fathers with diabetes (PT2D) were much older and had higher TC than those of mothers with diabetes (MT2D). After adjusting for gender of the parents, there was no difference between MT2D and PT2D on insulin sensitivity.

Conclusions: Inheritance if diabetes is associated with the decline of insulin sensitivity. In addition, insulin sensitivity declined with increasing WC and TG in FHD^+ subjects.

Introduction

The prevalence of diabetes, especially type 2 diabetes mellitus (T2DM), increases markedly throughout the world, including in China.[1] T2DM is characterized by both insulin resistance (IR) and β-cell dysfunction. Abnormalities in β-cell function are present in high-risk individuals long before they develop hyperglycemia.[2] This recognition has occurred in part because of a better understanding of the ability of the β cell to regulate its insulin response to stimuli based on differences in insulin sensitivity.

Because T2DM and its complications are associated with considerable socioeconomic burden and mortality, there is increasingly interest in developing strategies to prevent or delay progression of the disease.

In recent years, researchers have paid more attention to the so-called "prediabetic state" (i.e., impaired glucose regulation, including impaired fasting glucose and impaired glucose tolerance). Prospective studies showed that people in impaired glucose tolerance or impaired glucose regulation have significantly increased risk for both diabetes mellitus (DM)[3,4] and diabetes-related cardiovascular disease.[5–7] In clinical practice, we often find people with normal fasting and 2-h postprandial glucose levels but having a high level of 30-min plasma glucose (PG) or 60-min PG after an oral glucose tolerance test, which is closely related to early insulin secretion. Studies[8–10] have shown that such people had significantly increased risk for DM in this early stage of glucose intolerance.

In addition, IR has been one research focus of diabetes, such that the control strategies of T2DM have been changed from

[1]Department of Endocrinology, Fujian Provincial Hospital, Fujian Medical University, Fuzhou, China.
[2]Department of Endocrinology, North Branch of Fujian Provincial Hospital, Fuzhou, China.
[3]Department of Endocrinology, Fujian Provincial Geriatric Hospital, Fuzhou, China.
*The first four authors contributed equally to the study.

the "hypoglycemic therapy" into "improve the IR and IR-related metabolic abnormalities, and make a comprehensive prevention."[11] The homeostasis model assessment (HOMA) of IR, which is a useful surrogate index of IR in subjects with and without diabetes, is a mathematical assessment of the interaction between β-cell function and IR. That model is useful in clinical and epidemiologic studies and may be used to assess the response to antidiabetes drugs, to estimate the likelihood of cardiovascular disease in people with T2MD, and to evaluate the risk of diabetes. The HOMA of β-cell function (HOMA-β) is used to evaluate basic insulin secretion, and the HOMA-IR is used to assess insulin sensitivity.[12]

T2DM is attributed to both genetic and environmental factors. There is strong evidence that T2DM is genetically determined,[13,14] and the first-degree offspring of patients with T2DM are prone to develop T2DM that has both IR and β-cell impairment.[15] In only a small number of cases, however, is the inheritance pattern for the genetic defect resulting in T2DM well documented.[16,17] Previous studies of the heterogeneous disorder T2DM are from Western countries. Little is known about the impact of family history of diabetes (FHD) on β-cell function and IR among Chinese people with normal glucose tolerance (NGT). In this study we wanted to determine whether FHD will affect β-cell function and IR among Chinese people with NGT.

Research Design and Methods

Study population

Subjects registered were permanent residents 20 years of age or older in Fujian Province (population approximately 32 million). A multistage, stratified, cluster random sampling method was used in order to select a provincially representative sample of individuals from July 2007 to May 2008. A total sample size of 3,294 was registered. We excluded those whose data were not completed (PG levels were not measured at 0 and 30 min), whose arterial blood pressure was >140/90 mm Hg, serum total cholesterol (TC) was >7.8 mmol/L, serum triglycerides (TGs) were >4.6 mmol/L, and electrocardiogram showed abnormalities. Thus, 1,183 (406 males and 777 females) subjects with NGT were enrolled. All investigators received special training before the investigation, and all subjects signed informed consent authorized by the Diabetes Branch of the Chinese Medical Association.

Study design

All participants were asked to complete a standard questionnaire asking about age, gender, smoking status (past or present smoker, number of cigarettes smoked daily, and years of smoking), history of diabetes, history of cardiovascular disease (i.e., myocardial infarction, coronary artery bypass graft, coronary intervention therapy, heart failure, stroke, amputation history, hypertension, and whether under drug treatment), family history of hypertension, myocardial infarction, stroke, or DM. An FHD existed if one or both of the parents had diabetes. FHD^+ was defined as one of the parents had diabetes. Height and weight were measured without shoes and in light clothing. Body mass index (BMI) was calculated by dividing weight by height squared (kg/m^2). Waist circumference (WC) was measured at the middle point between the costal margin and iliac crests, and hip circumference was measured at the level of the trochanters. Waist–hip ratio (WHR) was calculated as the ratio of WC to hip circumference. Blood pressure was measured twice, in the sitting position, using a manual sphygmomanometer in the right arm, and the mean of the two readings was used for analysis.

Laboratory tests were taken from 5 mL of blood in a vacuum tube containing sodium fluoride from the subjects who had fasted for at least 10 h. All subjects except those previously diagnosed with T2DM were administered a 75-g oral glucose tolerance test. According to Chinese medical ethics, DM subjects accepted a 100-g steamed-bread test (a kind of standardized mixed meal test) as a surrogate, which equally contains 75 g of carbohydrate and was linearly related to values measured 2 h after an oral glucose tolerance test.[18] After 30 and 120 min, 5 mL of blood with anticoagulant was drawn from the subjects. Levels of blood glucose, TC, TGs, and high-density lipoprotein cholesterol (HDL-C) were tested using the glucose oxidase method, colorimetric enzyme assays, glycerol phosphate enzymatic oxidation assay, and end point colorimetry, respectively. Low-density lipoprotein cholesterol (LDL-C) was calculated by the formula of Friedewald et al.[19]

Assays

HOMA-IR is defined as (FPI×FPG)/22.5, where FPI is fasting plasma insulin concentration (mU/L) and FPG is fasting PG (mmol/L); this index, which largely reflects hepatic IR, has also been validated against the clamp. The equation for HOMA-β is (20×FPI)/(FPG – 3.5).[20] Insulin secretion also is assessed by the insulinogenic index (IGI) (ΔI30/ΔG30), where ΔI30 is the change in insulin from 0 to 30 min and ΔG30 is the change in glucose from 0 to 30 min, which is correlated with gold standard measures of insulin secretion (first-phase insulin secretion on intravenous glucose tolerance testing).[21] Disposition index (DI) is calculated to verify if insulin secretion compensates IR and is assessed byΔI30/ΔG30/HOMA-IR, which has been proposed by Bergman et al.[22] and Ryder et al.[23] using the principle of glucose DI. Plasma insulin was measured by double-antibody radioimmunoassay.

Inclusion criteria

Diagnosis of NGT was based on criteria published by the World Health Organization of FPG of <6.1 mmol/L and 2-h PG after glucose load of <7.8 mmol/L with no diagnosis of history of diabetes and impaired glucose regulation previously.[24] Diagnosis of hypertension was systolic blood pressure of >140 mm Hg and/or diastolic blood pressure of >90 mm Hg or having been diagnosed with hypertension or taking antihypertension treatment.

Statistical analysis

EpiData software (The EpiData Association, Odense, Denmark) was used to establish the database, and the statistical program SPSS version 13.0 (SPSS, Inc., Chicago, IL) was used for statistical analysis. Results are presented as mean ± SD values for normal distribution and median (95% confidence interval [CI]) for a skewed distribution. Independent-samples t test or nonparametric test was used to compare differences between subgroups when appropriate. Multiple

Table 1. Metabolic Characteristics of the Study Subjects

Categorical variable	*FHD$^+$ (n = 153)*	*FHD$^-$ (n = 1,030)*	P[a]
Age (years)	39.59 ± 8.68	40.57 ± 12.86	0.05
Weight (kg)	60.54 ± 10.18	58.80 ± 10.02	0.047
Height (cm)	161.29 ± 7.18	161.19 ± 7.99	0.874
Body mass index (kg/m^2)	23.19 ± 3.10	22.58 ± 3.16	0.025
Waist circumference (cm)	76.21 ± 9.59	76.62 ± 8.83	0.591
Waist to hip ratio	0.82 ± 0.70	0.83 ± 0.70	0.400
Blood pressure (mm Hg)			
Systolic	113.71 ± 14.71	115.23 ± 30.23	0.542
Diastolic	75.30 ± 9.67	75.11 ± 30.23	0.938
Plasma glucose (mmol/L)			
Fasting	4.70 ± 0.51	4.70 ± 0.54	0.958
30-min	7.91 ± 1.79	7.90 ± 1.81	0.598
2-h	5.42 ± 1.17	5.22 ± 1.17	0.052
Total cholesterol (mmol/L)	4.64 ± 1.00	4.46 ± 0.99	0.034
Triglycerides (mmol/L)	1.01 (0.39–10.47)	1.00 (0.22–14.79)	0.792
High-density lipoprotein (mmol/L)	1.29 ± 0.32	1.32 ± 0.35	0.397
Low-density lipoprotein (mmol/L)	2.75 ± 0.91	2.57 ± 0.82	0.029

Data are mean ± SD values or median (minimum and maximum) values as indicated. Differences between family history of diabetes (FHD) were compared for significance using independent-samples *t* test if variables were normal or nonparametric test if non-normal.
[a]*P* for positive FHD (FHD$^+$) versus negative FHD (FHD$^-$). *P* values of < 0.05 (two-tailed) were considered to be significant.

linear regression analysis, based on the data from all participants, was applied to control confounders. The odds ratio (OR) of effect of FHD on IR was analyzed by using logistic regression analysis. An OR value of >1 is regarded as a risk factor. All *P* values < 0.05 (two-tailed) were considered to be significant.

Results

In total, 1,183 subjects 20–74 years old were included into statistical analysis eventually. Of those, 406 were males (mean age, 39.0 years), and 777 were females (mean age, 41.0 years). The basic characteristics of subjects by FHD are shown in Table 1. We found that FHD$^+$ subjects had higher values of weight, BMI, LDL-C, and TC. Although HDL-C, WHR, and TG were risk factors for DM, there was no significance between the two groups.

Table 2 shows the mathematical assessment of β-cell function and IR of the study subjects. We found that there was no difference on β-cell insulin secretion function (independent-samples *t* test or nonparametric test on HOMA-β, IGI, and DI [$P > 0.05$ for all]) between the two groups. However, FHD$^+$ subjects had lower insulin sensitivity than FHD-negative (FHD$^-$) subjects; the 95% CI of the difference of HOMA-IR was 0.11–0.41. Subjects with FHD$^+$ showed higher risk of IR after adjusting for other risk factors (OR 1.523 [1.272–2.009] by the method of logistic regression). After adjusting for other classical DM risk factors, including weight, BMI, WC, hip circumference, WHR, HDL-C, LDL-C, TC, and TGs, multiple linear regression analysis showed that only WC and TGs had significantly impact on insulin sensitivity ($P < 0.05$ for both) in FHD$^+$ subjects (Table 3), and the insulin sensitivity decreased with increasing WC and TGs. The basic characteristics of the FHD$^+$ subjects by gender of the parents are shown in Table 4. We found that age distribution and TC were different between the two groups. Offspring of fathers with diabetes (PT2D) were much older and had higher TC than offspring of mothers with diabetes (MT2D). After adjusting for gender of the parents, there was no difference between MT2D and PT2D effect on insulin sensitivity.

Table 2. Mathematical Assessment of β-Cell Function and Insulin Resistance of the Study Subjects

	FHD$^+$ (n = 153)	*FHD$^-$ (n = 1,030)*	P[a]
HOMA-IR	1.75 ± 1.59	1.49 ± 0.71	0.001
HOMA-β	142.30 ± 846.24	152.86 ± 152.28	0.878
IGI	14.84 ± 45.90	34.33 ± 247.05	0.332
DI	11.30 ± 33.17	20.97 ± 99.76	0.237

Homeostasis model assessment of insulin resistance (HOMA-IR) is used to assess insulin sensitivity. Homeostasis model assessment of β-cell function (HOMA-β) is used to evaluate basic insulin secretion. Insulinogenic index (IGI) is also used to evaluate insulin secretion. Disposition index (DI) is calculated to verify if insulin secretion compensate insulin resistance.
[a]*P* for positive FHD (FHD$^+$) versus negative FHD (FHD$^-$). *P* values of < 0.05 (two-tailed) were considered to be significant.

Discussion

The present study investigated the relationship of FHD with β-cell function in a large population ($n = 1,183$) of individuals from Fujian Province. This study reached the following conclusions: (1) The FHD$^+$ subjects were less insulin

Table 3. Covariates Included in Multiple Linear Regression

Covariate	*Standardized coefficient (β)*	*Significance*	*95% confidence interval of β*	
			Lower	*Upper*
WC	0.119	0.000	0.0102	0.0298
TGs	0.097	0.001	0.0568	0.2292

P values of < 0.05 (two-tailed) were considered to be significant.
TGs, triglycerides; WC, waist circumference.

Table 4. Sex-Stratified Characteristics of Subjects with Mothers Versus Fathers Having Type 2 Diabetes Mellitus

	MT2D (n = *78*)	*PT2D* (n = *75*)	P[a]
Age (years)	41.28 ± 8.89	37.83 ± 8.14	0.013
Weight (kg)	61.27 ± 9.74	59.78 ± 10.63	0.452
Height (cm)	161.72 ± 7.18	160.85 ± 7.21	0.368
Body mass index (kg/m^2)	23.35 ± 2.85	23.02 ± 3.35	0.504
Waist to hip ratio	0.82 ± 0.60	0.83 ± 0.78	0.556
Blood pressure (mm Hg)			
Systolic	114.60 ± 14.98	112.79 ± 14.47	0.447
Diastolic	75.90 ± 9.78	74.68 ± 9.58	0.438
Plasma glucose (mmol/L)			
Fasting	4.76 ± 0.53	4.63 ± 0.49	0.122
30-min	8.15 ± 1.59	7.81 ± 1.77	0.217
2-h	5.46 ± 1.12	5.38 ± 1.22	0.672
Total cholesterol (mmol/L)	4.66 ± 0.97	4.24 ± 0.96	0.009
Triglycerides (mmol/L)	1.08 (0.44–10.47)	0.97 (0.39–4.86)	0.289
High-density lipoprotein (mmol/L)	1.32 ± 0.33	1.26 ± 0.32	0.270
Low-density lipoprotein (mmol/L)	2.68 ± 0.78	2.47 ± 0.86	0.109
HOMA-IR	1.51 ± 0.71	1.47 ± 0.72	0.746
HOMA-β	159.97 ± 166.84	145.47 ± 133.93	0.555
IGI	13.31 ± 14.37	56.20 ± 352.43	0.285
DI	10.24 ± 11.50	32.12 ± 141.63	0.186

Data are mean ± SD values or median (minimum and maximum) values as indicated. Differences between maternal type 2 diabetes mellitus (MT2D) and paternal type 2 diabetes mellitus (PT2D) were compared for significance using independent-samples *t* test if variables were normal or nonparametric test if non-normal.

[a]*P* for MT2D versus PT2D. *P* values of < 0.05 (two-tailed) were considered to be significant.

DI, disposition index; HOMA-β, homeostasis model assessment of β-cell function; HOMA-IR, homeostasis model assessment of insulin resistance; IGI, insulinogenic index.

sensitive and displayed higher values of weight, BMI, LDL-C, and TC, but adjusting for other risk factors, multiple linear regression analysis showed that these factors have no statistical significance on insulin sensitivity ($P > 0.05$). (2) WC and TGs were independent risk factors of decreasing of insulin sensitivity among the FHD$^+$ subjects. We suggest that early preventive strategies are necessary for the FHD$^+$ group.

Several studies have suggested that the first-degree offspring of T2DM patients showed IR and β-cell dysfunction in response to oral glucose challenge.[15,25] In our study, we found that FHD$^+$ was a predictor of insulin sensitivity in the NGT subjects. This was consistent with a previous study[26] that showed that positive family history was a strong predictor of severe hyperglycemia in both Melanesian and Indian groups. We note that BMI, LDL-C, and TC had no statistically significant effect on insulin sensitivity ($P > 0.05$) in our study after adjusting for other risk factors. This was inconsistent with some studies.[27,28] We thought the main reason was that we excluded the abnormal subjects with these factors. The Relationship between Insulin Sensitivity and Cardiovascular Disease Investigators study in Europe suggested that insulin sensitivity was accentuated along maternal inheritance.[28] However, our study showed that there was no difference in insulin sensitivity and β-cell insulin secretion function in the offspring between the paternal and maternal inheritance; differences in ethnic background, environment, and lifestyle factors may account for this disparity. In addition, in our study, there was no significant difference on first-phase insulin secretion between the two groups, which was contrast to the study that suggested the offspring of T2DM had impaired first-phase insulin secretion.[23] We used IGI to assess first-phase insulin secretion, which was different from the euglycemic hyperinsulinemic clamp technique the previous study used. We characterized β-cell function by using a mathematical model. The model retains the known constitutive characteristics of β-cell secretory function: the ability to respond to glucose in a dose–response fashion, the ability to respond rapidly to a rapid glucose increase (represented by the rate component), and the ability to potentiate the secretory response during sustained hyperglycemia or after release of incretin hormones. This model has been proved effective in previous applications.[29–33]

It should be noted that weight, WC, TGs, and dyslipidemia are risk factors leading to IR in FHD$^+$ subjects in our study, which was consistent with the study suggesting that Brazilian adolescents with two or more risk factors—family history of T2DM, obesity, hypertension, dyslipidemia, or polycystic ovary syndrome—for the development of T2DM have higher IR and lower insulin sensitivity.[34] So it is important to prevent these risk factors in clinical practice.

A survey among the noninstitutionalized U.S. civilian population considered adults with diabetes and a higher familial risk of diabetes have a worse glycemic control and higher TGs.[35] In our study, we found the FHD$^+$ subjects with NGT in China also had higher TG levels, with decreasing insulin sensitivity. Both of these studies concluded that TG levels should be controlled early in FHD$^+$ subjects with or without diabetes. Moreover, a recent cross-sectional study on risk factors of T2DM among adults in Beijing recommended that it was of great importance to carry out prevention and control programs for T2DM to eliminate the risk factors among adults, such as keeping weight within the normal range and decreasing TG and cholesterol levels.[36] We reviewed published articles and found two studies, one in

Malaysia[37] and one in Japan,[38] demonstrating that WC may be a better indicator for the prediction of obesity-related diabetes risk factors in men and women, and our result was consistent with these findings.

In our study, the *P* value of WC and TGs between FHD^+ and FHD^- subjects showed no significant difference, and FHD^+ subjects showed a higher risk of IR after adjusting for other risk factors (OR 1.523 [1.272–2.009]), so we think the decreased insulin sensitivity in FHD^+ patients is the result of the FHD^+.

In diabetes prevention, clinic doctors emphasize diet and lifestyle factors. The diffusion of "genetic risk" has little impact on doctor–patient interactions, but can be clearly seen in academic research, government policy, and medical specialties, raising concerns about whether or not interventions will be directed at the social determinants of this growing health concern. It has been suggested that T2DM has a strong genetic basis and mitochondrial DNA mutations.[39] Our results also support a recent study examining the association between parental history of T2DM and glycemic control.[40] So we conclude that obtaining the family history of the disease is crucial in identifying and targeting high-risk patients with diabetes who may require more stringent lifestyle changes as well as pharmaceutical intervention.

Certain limitations in our study were as follows. First, the accuracy of the information on parental diabetes is crucial for this kind of study. Although parents were not interviewed nor were their biochemical data verified directly, questionnaires were completed by the investigator, who had been trained to obtain such information as accurately as possible. Therefore, information on parental diabetes retrieved from the offspring was reliable. Second, estimating insulin sensitivity only in the mathematical assessment model has poor accuracy. Although the β-cell exhibits such a complex behavior that all models are necessarily approximate, β-cell models, which as empirical β-cell function indexes do not bear a clear relation to β-cell physiology, are nevertheless indispensible tools for the analysis of β-cell function, and this applies to large-sample epidemiological studies. Therefore, it is reasonable to use the mathematical assessment model as a simple IR risk index. If this calculation is combined with insulin levels, the appropriate evaluation should be more comprehensive. There is also room for improvement and exploration of other areas in our future research.

In summary, FHD^+ will lead to decreased insulin sensitivity in NGT subjects, and IR can drive the occurrence and progress of T2DM. Therefore, attention should be paid to individuals with FHD^+ in diabetes prevention studies.

Acknowledgments

This work was supported by grants C071002 and 2009Y0011 from the Natural Science Foundation of Fujian Province of China.

Author Disclosure Statement

No competing financial interests exist. G.C. contributed to the study design and discussion and reviewed/edited the manuscript. M.L. researched data and wrote the manuscript. Y.X. edited the manuscript and researched data. N.C. reviewed/edited the manuscript. H.H., J.L., L. Li, L. Lin, and J.Y. researched data. J.W. contributed to the discussion.

References

1. Ning G, Hong J, Bi Y, Gu W, Zhang Y, Zhang Z, Huang Y, Wang W, Li X: Progress in diabetes research in China. J Diabetes 2009;1:163–172.
2. Kahn SE: The relative contributions of insulin resistance and β cell dysfunction to the pathophysiology of type 2 diabetes. Diabetologia 2003;46:3–19.
3. Fang FS, Tian H, Li CL, Shao YH, Li J, Zhong WW, Liu MY, Yan ST, Yang G, Cheng XL, Ma Q, Wang HX: The clinical characteristics and trend of conversion to type 2 diabetes mellitus of individuals with normal glucose tolerance-hyperinsulinemia [in Chinese]. Zhonghua Nei Ke Za Zhi 2010;49:480–483.
4. Rhee SY, Woo JT, Chon S, Hwang YC, Oh S, Ahn KJ, Chung HY, Kim SW, Kim JW, Kim YS: Characteristics of insulin resistance and insulin secretory capacity in Korean subjects with IFG and IGT. Diabetes Res Clin Pract 2010;89:250–255.
5. Meigs JB, Nathan DM, D'Agostino RB Sr, Wilson PW; Framingham Offspring Study: Fasting and postchallenge glycemia and cardiovascular disease risk: the Framingham Offspring Study. Diabetes Care 2002;25:1845–1850.
6. DECODE Study Group, the European Diabetes Epidemiology Group: Glucose tolerance and cardiovascular mortality: comparison of fasting and 2-hour diagnostic criteria. Arch Intern Med 2001;161:397–405.
7. Pan WH, Cedres LB, Liu K, Cedres LB, Liu K, Dyer A, Schoenberger JA, Shekelle RB, Stamler R, Smith D, Collette P, Stamler J: Relationship of clinical diabetes and asymptomatic hyperglycemia to risk of coronary heart disease mortality in men and women. Am J Epidemiol 1986;123: 504–516.
8. Weyer C, Tataranni PA, Bogardus C, Pratley RE: Insulin resistance and insulin secretory dysfunction are independent predictors of worsening of glucose tolerance during each stage of type 2 diabetes development. Diabetes Care 2000; 24:89–94.
9. Bunt JC, Krakoff J, Ortega E, Knowler WC, Bogardus C: Acute insulin response is an independent predictor of type 2 diabetes mellitus in individuals with both normal fasting and 2-h plasma glucose concentrations. Diabetes Metab Res Rev 2007;23:304–310.
10. Abdul-Ghani MA, Williams K, DeFronzo RA, Stern M: What is the best predictor of future type 2 diabetes? Diabetes Care 2007;30:1544–1548.
11. Zheng H, Ge Y: Research progress on IR improvement and acting mechanisms of active ingredients of traditional Chinese medicine [in Chinese]. Zhongguo Zhong Yao Za Zhi 2010;35:531–535.
12. Wallace TM, Levy JC, Matthews DR: Use and abuse of HOMA modeling. Diabetes Care 2004;27:1487–1495.
13. Barnett AH, Eff C, Pyke DA: Diabetes in identical twins: a study of 200 pairs. Diabetes 1981;20:87–93.
14. Newman B, Selby JV, King MC, Slemenda C, Fabsitz R, Friedman GD: Concordance for type II (non-insulin dependent) diabetes mellitus in male twins. Diabetologia 1987;30: 763–768.
15. Vauhkonen I, Niskanen L, Vanninen E, Kainulainen S, Uusitupa M, Laakso M: Defects in insulin secretion and insulin action in non-insulin-dependent diabetes mellitus are inherited. Metabolic studies on offspring of diabetic probands. J Clin Invest 1998;101:86–96.
16. Froguel P, Zouali H, Vionnet N, Velho G, Vaxillaire M, Sun F, Lesage S, Stoffel M, Takeda J, Passa P, Permutt MA, Beckmann JS, Bell GI, Cohen D: Familial hyperglycemia due

to mutations in glucokinase. Definition of subtype of diabetes mellitus. N Engl J Med 1993;328:697–702.
17. van den Ouweland JMW, Lemkes HH, Ruitenbeek W, Sandkuijl LA, de Vijlder MF, Struyvenberg PA, van de Kamp JJ, Maassen JA: Mutation in mitochondrial tRNA Leu(UUR) gene in a large pedigree with maternally transmitted type II diabetes mellitus and deafness. Nat Genet 1992;1:368–371.
18. Wolever TM, Chiasson JL, Csima A, Hunt JA, Palmason C, Ross SA, Ryan A: Variation of postprandial plasma glucose, palatability, and symptoms associated with a standardized mixed test meal versus 75 g oral glucose. Diabetes Care 1998; 21:336–340.
19. Friedewald WT, Levy RI, Fredrickson DS: Estimation of the concentration of low-density lipoprotein cholesterol in plasma without use of the preparative ultracentrifuge. Clin Chem 1972;18:499–502.
20. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC: Homeostasis model assessment: insulin resistance and β-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985;28:412–419.
21. Wareham NJ, Phillips DI, Byrne CD, Hales CN: The 30 minute insulin incremental response in an oral glucose tolerance test as a measure of insulin secretion. Diabet Med 1995;12:931–934.
22. Bergman RN, Pillip LS, Cobelli O: Physiological evaluation of factors controlling glucose tolerance in man: measurement of insulin sensitivity and β cell glucose sensitivity from the response of intravenous glucose. J Clin Invest 1981;68:1456–1467.
23. Ryder E, Gómez M, Fernández V, Campos G, Morales LM, Valbuena H, Raleigh X: Presence of impaired insulin secretion and insulin resistance in normoglycemic male subjects with family history of type 2 diabetes. Diabetes Res Clin Pract 2003;60:95–103.
24. Alberti KGMM, Zimmet PZ: Definition diagnosis and classification of diabetes mellitus and its complications. Part 1. Diagnosis and classification of diabetes mellitus: provisional report of a WHO consultation. Diabet Med 1998;15:539–553.
25. Stadler M, Pacini G, Petrie J, Luger A, Anderwald C; RISC Investigators: Beta cell (dys)function in non-diabetic offspring of patients with diabetes. Diabetologia 2009;52:2435–2444.
26. Hoskins PL, Handelsman DJ, Hannelly T, Silink M, Yue DK, Turtle JR: Diabetes in the Melanesian and Indian peoples of Fiji: a study of risk factors. Diabetes Res Clin Pract 1987;3: 269–276.
27. Qu HQ, Li Q, Rentfro AR, Fisher-Hoch SP, McCormick JB: The definition of insulin resistance using HOMA-IR for Americans of Mexican descent using machine learning. PLoS One 2011;6:e21041.
28. Natali A, Muscelli E, Mari A, Balkau B, Walker M, Tura A, Anderwald C, Golay A, Ferrannini E; Relationship between Insulin Sensitivity and Cardiovascular Disease Investigators: Insulin sensitivity and β cell function in the offspring of type 2 patients with diabetes: impact of line of inheritance. J Clin Endocrinol Metab 2010;95:4703–4711.
29. DeFronzo R, Gastaldelli A, Miyazaki Y, Matsuda M, Mari A, Ferrannini E: Critical evaluation of insulin secretion in NGT, IGT, and T2DM subjects [abstract]. Diabetes 2003;52:A335.
30. Ferrannini E, Gastaldelli A, Miyazaki Y, Matsuda M, Pettiti M, Natali A, Mari A, DeFronzo RA: Predominant role of reduced β-cell sensitivity to glucose over insulin resistance in impaired glucose tolerance. Diabetologia 2003;46:1211–1219.
31. Ferrannini E, Mari A: Beta cell function and its relation to insulin action in humans: a critical appraisal. Diabetologia 2004;47:943–956.
32. Mari A, Schmitz O, Gastaldelli A, Oestergaard T, Nyholm B, Ferrannini E: Meal and oral glucose tests for the assessment of β-cell function: modeling analysis in normal subjects. Am J Physiol Endocrinol Metab 2002;282:E1159–E1166.
33. Mari A, Tura A, Gastaldelli A, Ferrannini E: Assessing insulin secretion by modeling in multiple-meal tests: role of potentiation. Diabetes 2002;51(Suppl 1):S221–S226.
34. Silva RC, Miranda WL, Chacra AR, Dib SA: Insulin resistance, beta-cell function, and glucose tolerance in Brazilian adolescents with obesity or risk factors for type 2 diabetes mellitus. J Diabetes Complications 2007;21:84–92.
35. Kuo CK, Lin LY, Yu YH, Chang CH, Kuo HK: A family history of diabetes mellitus is associated with poor glycemic control and increased metabolic risks among people with diabetes: data from the National Health and Nutrition Examination Survey 1999–2004. Intern Med 2010;49:549–555.
36. Zhang J, Dong Z, Li G, Jiao SF, Xie J, Zhou Y, Zhao Y, Yang XW, Yang WN: A cross-sectional study on risk factors of associated type 2 diabetes mellitus among adults in Beijing [in Chinese]. Zhonghua Liu Xing Bing Xue Za Zhi 2011; 32:357–360.
37. Zaher ZM, Zambari R, Pheng CS, Muruga V, Ng B, Appannah G, Onn LT: Optimal cut-off levels to define obesity: body mass index and waist circumference, and their relationship to cardiovascular disease, dyslipidaemia, hypertension and diabetes in Malaysia. Asia Pac J Clin Nutr 2009;18:209–216.
38. Sakurai M, Miura K, Takamura T, Ishizaki M, Morikawa Y, Nakamura K, Yoshita K, Kido T, Naruse Y, Kaneko S, Nakagawa H: J-shaped relationship between waist circumference and subsequent risk for Type 2 diabetes: an 8-year follow-up of relatively lean Japanese individuals. Diabet Med 2009;26:753–759.
39. Momiyama Y, Suzuki Y, Ohsuzu F, Atsumi Y, Matsuoka K, Kimura M: Maternally transmitted susceptibility to non-insulin-dependent diabetes mellitus and left ventricular hypertrophy. J Am Coll Cardiol 1999;33:1372–1378.
40. Gong L, Kao WH, Brancati FL, Batts-Turner M, Gary TL: Association between parental history of type 2 diabetes and glycemic control in urban African Americans. Diabetes Care 2008;31:1773–1776.

Address correspondence to:
Gang Chen, M.D., Ph.D.
Department of Endocrinology
Fujian Provincial Hospital
Fujian Medical University
Box 4-704
92 Huqian Road
Fuzhou, Fujian, China

E-mail: chengang18@yahoo.com

or

Junping Wen, M.D.
Department of Endocrinology
Fujian Provincial Hospital
Fujian Medical University
Box 4-704
92 Huqian Road
Fuzhou, Fujian, China

E-mail: wenjunping@medmail.com.cn