Relative Contribution of Insulin Sensitivity and β-Cell Function to Plasma Glucose and Insulin Concentrations During the Oral Glucose Tolerance Test

Ken C. Chiu, Dorothy S. Martinez, Carol Yoon, and Lee-Ming Chuang

Plasma glucose and insulin concentrations have been used in genetic studies as quantitative phenotypic traits and also as surrogates for insulin sensitivity and β-cell function. However, the significance of these traits in relation to insulin sensitivity and β-cell function was unknown. We examined how insulin sensitivity and β-cell function affected plasma glucose and insulin concentrations during the oral glucose tolerance test (OGTT). This is a cross-sectional study enrolling 105 glucose-tolerant subjects (64 females; age, 18 to 40 years; body mass index, 17.58 to 37.57 kg/m^2; waist-to-hip ratio, 0.649 to 1.033 cm/cm). They participated in both OGTTs and hyperglycemic clamps. The relationship between plasma glucose and insulin concentrations and indices of insulin sensitivity and β-cell function was examined. Univariate analyses showed that insulin sensitivity index (ISI) had some influence on plasma insulin concentrations (r^2 = .2623 to .3814) during the OGTT; however, it had only modest impacts on plasma glucose levels at 60, 90, and 120 minutes (r^2 = .0537 to .1300). Neither first phase (1stIR) nor second phase insulin response (2ndIR) affected plasma glucose concentrations. Multivariate analyses showed an independent impact (all $P < .0001$) of ISI on plasma glucose concentrations at 60, 90, and 120 minutes and on plasma insulin concentrations at every time point except at 30 minutes. Except for plasma insulin concentration at 30 minutes, of which 24% of the variation can be explained by 1stIR, β-cell function (either 1stIR or 2ndIR) only had a very modest impact on 30-, 60-, 90- and 120-minute plasma glucose concentrations and on plasma insulin concentration at 60 minutes. In glucose-tolerant subjects, ISI plays an important role in determining postchallenged plasma glucose concentrations at 60, 90, and 120 minutes, as well as plasma insulin concentrations at fasting, 60, 90, and 120 minutes. However, β-cell function is only reflected in plasma insulin concentration at 30 minutes through 1stIR. Therefore, we conclude that it is essential to measure β-cell function in vivo if one plans to study the genetic influence of β-cell dysfunction.

SEVERAL LINES OF evidence demonstrate the essential importance of genetic factors in the etiologies of type 2 diabetes mellitus (also known as non–insulin-dependent diabetes mellitus [NIDDM]). These data include the high prevalence of a positive family history,[1] marked differences in prevalence among various racial groups,[2] and differential concordance rates between monozygotic and dizygotic twins.[3-6] Furthermore, studies on Pima Indians and Caucasians show familial clustering of insulin resistance,[7,8] which is 1 of the key features of NIDDM. Also, segregation studies showed that 30% to 45% of insulin sensitivity was inherited.[9-11] Thus, genetic susceptibility is almost an invariable requirement for the development of the disease, and insulin sensitivity appears to be an inherited trait. Similarly, defective β-cell function is also apparent in nondiabetic offspring from diabetic parents,[12] and β-cell function is also demonstrated to be an inherited trait.[9,11] Identifying the causative genes will likely lead to novel methods of therapy and prevention and will hopefully help to alleviate the financial burden of NIDDM and its complications.

It is generally acknowledged that NIDDM is not a single gene disease, but rather a genetically heterogeneous group of metabolic disorders that share glucose intolerance as a result of the imbalance between insulin sensitivity and β-cell function.[13] However, measurements of insulin sensitivity and β-cell function are not only labor intensive, but also time consuming. Therefore, plasma glucose and insulin concentrations at fasting and after a glucose challenge have been used as phenotypic traits in genetic studies. Despite the wide-spread use of these traits in both rodents and human, there is very little information available regarding how insulin sensitivity and β-cell function affect plasma glucose and insulin concentrations at each time point during a standard oral glucose tolerance test (OGTT).

This study is designed to investigate the relative contribution of insulin sensitivity and β-cell function to plasma glucose and insulin concentrations during an OGTT. Arterial blood pressure levels are higher in insulin-resistant subjects than in insulin-sensitive normotensive subjects[14]; conversely, insulin sensitivity is impaired in nondiabetic subjects with essential hypertension.[15] In addition, hyperglycemia per se has a detrimental effect on both insulin sensitivity and β-cell function.[16] Therefore, we examined the relationship between plasma glucose and insulin concentrations during the OGTT and the indices of insulin sensitivity and β-cell function in normotensive and glucose-tolerant subjects.

SUBJECTS AND METHODS

Study Subjects

The recruitment of subjects was performed as described previously.[17] This study included 105 glucose-tolerant and normotensive subjects. Briefly, to minimize confounding factors, only healthy sub-

From the Division of Endocrinology, Diabetes and Hypertension, Department of Medicine, University of California, Los Angeles, School of Medicine, Los Angeles, CA; and the Department of Internal Medicine and Graduate Institute of Clinical Medicine, National Taiwan University Hospital, Taipei, Taiwan.

Submitted March 26, 2001; accepted July 16, 2001.

Supported in part by Grants No. MO1RR00865 from United States Public Health Service (USPHS) (to UCLA-General Clinical Research Center [GCRC]), RO1DK52337-01 from the National Institutes of Health/National Institute of Diabetes and Digestive and Kidney Diseases (NIH/NIDDK) (to K.C.C.), Diabetes Action Research and Education Foundation (to K.C.C.), and the American Diabetes Association (to K.C.C.).

Address reprint requests to Ken C. Chiu, MD, FACE, 675 Charles E. Young Dr, South, 4629 MacDonald Research Laboratories, Los Angeles, CA 90095-7097.

0026-0495/02/5101-0018$35.00/0
doi:10.1053/meta.2002.29027

jects who received no regular medical treatments were invited to undergo a screening test as outpatients after an overnight fast. A standard OGTT with 75 g glucose was given with a brief physical examination. To exclude the secondary influence of insulin sensitivity and β-cell function from abnormal glucose tolerance,[16] only those who were noted to be glucose tolerant (fasting plasma glucose $<$ 6.1 mmol/L, interval plasma glucose $<$ 11.1 mmol/L, and 2-hour plasma glucose $<$ 7.7 mmol/L) were invited back for the assessment of β-cell function and insulin sensitivity using a hyperglycemic clamp technique. Because hypertension has been shown to be associated with insulin resistance,[15] only normotensive ($<$ 140/90 mm Hg) subjects were enrolled into the study. For safety reasons, anemic (hemoglobin $\leq$ 11.0 g/dL) subjects were also excluded from the hyperglycemic clamp of the study. To minimize the effect of smoking, they were asked to refrain from smoking for at least 12 hours before the study. After fasting and resting overnight in the General Clinical Research Center (GCRC) of this institution, participants received a bolus of 50% dextrose solution based on their body surface area (11.4 gm/m^2) at T=0 minute. Continuous infusion of 30% dextrose solution was commenced at T=15 minutes at variable rates, which were adjusted every 5 minutes based on the prevailing plasma glucose levels to maintain a plasma glucose level around 10 mmol/L towards T=180 minutes using the negative feedback principle.[18] Insulin sensitivity index (ISI), first phase insulin response (1stIR), and second phase insulin response (2ndIR) were calculated as before.[17] To correct the mass effect of plasma glucose on glucose uptake, we also calculated glucose clearance (G_{Cl}) as ISI divided by the plasma glucose concentration. The study was approved by the Human Subject Protection Committee of this institution. Written informed consent was obtained from all participants before entering the study. We confirm that the study has complied with the recommendations of the Declaration of Helsinki.

Statistical Analysis

The continuous variables with skewed distribution (age, body mass index, waist-to-hip ratio, plasma insulin levels, ISI, 1stIR, 2ndIR, and G_{Cl}), were logarithmically transformed before analysis. The relationship between variables were analyzed by simple regression (univariate analysis). A nominal *P* value less than .05 was considered significant. To examine the influence of multiple covariates on plasma glucose and insulin concentrations, multivariate analysis using general linear models was performed by considering age, gender, ethnicity, body mass index, waist-to-hip ratio, systolic blood pressure, diastolic blood pressure, 1stIR, 2ndIR, and ISI. A backward stepwise option with alpha-to-enter of 0.10 and alpha-to-remove of 0.10 was used to exclude covariates that had much less or no influence on the parameter under analysis. The covariates were removed 1 at a time, starting from the 1 that had the least impact, based on the *P* value (the highest *P* value). Stepwise regression analysis was stopped when all *P* values of all the remaining covariates were less than .10. SYSTAT 8.0 for Windows from SPSS, (Chicago, IL) was used for the statistical analyses.

RESULTS

This study included 105 subjects (64 females; age, 26 $\pm$ 1 years; body mass index, 24.79 $\pm$ 0.44 kg/m^2; waist-to-hip ratio, 0.793 $\pm$ 0.007 cm/cm; arithmetic mean $\pm$ standard error). Although all the participants were normotensive and glucose tolerant, there was a wide range of the variations in ISI (1.363 to 17.994 mmol/L/m^2/min/pmol/L), 1stIR (465 to 7,415 pmol/L), and 2ndIR (104 to 1,567 pmol/L). Because they were glucose tolerant, 1stIR and 2ndIR were correlated with ISI (r^2 = .3289, $P < .000001$ and r^2 = .5548, $P < .000001$, respectively) to maintain plasma glucose concentration within the normal range.

Univariate analyses (Table 1) showed that ISI contributed to variance of plasma insulin concentrations at every time point during the OGTT (r^2 = .2623 to .3814, all $P < .0001$). Although it had the least impact on plasma insulin concentration at 30 minutes, it remained explaining 26.23% of the variation. 1stIR had a strong influence on plasma insulin concentrations at fasting, 30, and 60 minutes (r^2 = .1643 to .3409, all $P < .0001$), while its influence on plasma insulin concentrations at 90 and 120 minutes was modest (r^2 = .0464, P = .0273 and r^2 = .0961, P = .0012, respectively). 2ndIR had a strong influence on plasma insulin concentrations at every time

Table 1. Univariate Analysis of Plasma Glucose and Concentrations During the OGTT

	Fasting	30 Minutes	60 Minutes	90 Minutes	120 Minutes	
Plasma glucose						
ISI	.0007	.0004	.0537	.0547	.1300	r^2
	−.0173	−.0370	−.5084	−.5062	−.6312	Coefficient
	.7831	.8452	.0174	.0164	.0002	*P*
1st IR	.0026	.0131	.0095	.0123	.0100	r^2
	.0338	−.2285	−.2226	−.2497	.1815	Coefficient
	.6054	.2446	.3215	.2593	.3108	*P*
2nd IR	.0000	.0003	.0014	.0000	.0310	r^2
	.0035	−.0310	−.0910	−.0160	.3373	Coefficient
	.9594	.8815	.7018	.9456	.0725	*P*
Plasma insulin						
ISI	.3140	.2623	.3352	.3077	.3814	r^2
	−.5603	−.5122	−.5790	−.5547	−.6175	Coefficient
	<.0001	<.0001	<.0001	<.0001	<.0001	*P*
1st IR	.1643	.3409	.2042	.0464	.0961	r^2
	.4054	.5838	.4519	.2154	.3099	Coefficient
	<.0001	<.0001	<.0001	.0273	.0012	*P*
2nd IR	.2139	.2611	.1452	.1178	.1905	r^2
	.4625	.5110	.3811	.3431	.4364	Coefficient
	<.0001	<.0001	<.0001	.0003	<.0001	*P*

point (r^2 = .1452 to .2611, all $P < .0001$) except at 90 minutes (r^2 = .1,178, $P = .0003$).

In glucose-tolerant subjects, a dynamic state between insulin sensitivity and β-cell function has to be kept to maintain glucose homeostasis. As a result, ISI, 1stIR, and 2ndIR were tightly and mutually correlated. ISI accounts for 32.89% of the variation in 1stIR ($P < .000001$) and 55.48% of the variation in 2ndIR ($P < .000001$); and 1stIR accounts for 47.66% of the variation in 2ndIR ($P < .000001$). Furthermore, numerous covariates (such as gender, age, body mass index, waist-to-hip ratio, systolic, and diastolic blood pressure) could also affect plasma insulin concentrations. Therefore, multivariate analysis was used to examine the interaction between these covariates, including ISI, 1stIR, and 2ndIR (Tables 2 and 3).

For plasma glucose concentrations, ISI had an independent effect at 60, 90, and 120 minutes ($P < .0001$ for each of the 3 time points), but no influence on plasma glucose concentration at fasting and 30 minutes ($P = .7867$ and $P = .6662$, respectively), as shown in Table 2. Although it was not detected by univariate analyses, 1stIR had an independent, but modest, influence on plasma glucose concentrations at 30, 60, and 90 minutes ($P = .0478$, $P = .0298$, and $P = .0015$, respectively). However, 1stIR had no independent influence on plasma glucose concentration at fasting and at 120 minutes ($P = .9260$ and $P = .7,189$, respectively). 2ndIR had an independent, but modest, influence on plasma glucose concentrations at 60 and 120 minutes ($P = .0298$ and $P = .0271$, respectively), while it had no influence on plasma glucose concentrations at fasting, 30, and 90 minutes ($P = .7587$, $P = .7055$, and $P = .1141$, respectively).

For fasting plasma insulin concentrations, 39.62% of the variation could be explained by ISI ($P < .0001$), body mass index ($P = .0084$), and systolic blood pressure ($P = .0780$), as shown in Table 3. 1stIR ($P < .0001$) was the key covariate for plasma insulin concentration at 30 minutes and along with waist-to-hip ratio ($P = .0022$), age ($P = .0034$), gender ($P = .0137$), and systolic blood pressure ($P = .0743$) accounted for 44.07% of the variation. Although ISI ($P < .0001$), 1stIR ($P = .0089$), and 2ndIR ($P = .0358$) accounted for 38.42% of the variation in plasma insulin concentration at 60 minutes, ISI (r^2 = .1709) played the key role compared with 1stIR (r^2 =

Table 2. Stepwise Multivariate Analyses of Plasma Glucose Concentrations During the OGTT

Dependent Variable	Covariate Entered*	r^2	P
Fasting plasma glucose			
	Body mass index	.0695	.0036
	Gender	.0597	.0069
	Diastolic blood pressure	.0232	.0884
Plasma glucose at 30 min			
	Waist-to-hip ratio	.0920	.0009
	Ethnicity	.0971	.0087
	Systolic blood pressure	.0388	.0290
	1st IR	.0317	.0478
Plasma glucose at 60 min			
	ISI	.1947	<.0001
	Gender	.0444	.0166
	1st IR	.0364	.0298
	Age	.0333	.0375
	2nd IR	.0218	.0911
Plasma glucose at 90 min			
	ISI	.1319	<.0001
	1st IR	.0896	.0015
Plasma glucose at 120 min			
	ISI	.1529	<.0001
	Systolic blood pressure	.0850	.0012
	Diastolic blood pressure	.0426	.0203
	2nd IR	.0385	.0271

*The following covariates were considered: age, gender, ethnicity, body mass index, waist-to-hip ratio, systolic blood pressure, diastolic blood pressure, 1st phase insulin response, 2nd phase insulin response, and insulin sensitivity index.

Table 3. Stepwise Multivariate Analyses of Plasma Insulin Concentrations During the OGTT

Dependent Variable	Covariate Entered*	r^2	P
Fasting plasma insulin			
	ISI	.2159	<.0001
	Body mass index	.0432	.0084
	Systolic blood pressure	.0189	.0780
Plasma insulin at 30 min			
	1st IR	.2409	<.0001
	Waist-to-hip ratio	.0560	.0022
	Age	.0509	.0034
	Gender	.0356	.0137
	Systolic blood pressure	.0184	.0743
Plasma insulin at 60 min			
	ISI	.1709	<.0001
	1st IR	.0434	.0089
	2nd IR	.0276	.0358
Plasma insulin at 90 min			
	ISI	.3077	<.0001
Plasma insulin at 120 min			
	ISI	.3191	<.0001
	Gender	.0274	.0321

*The following covariates were considered: age, gender, ethnicity, body mass index, waist-to-hip ratio, systolic blood pressure, diastolic blood pressure, 1st phase insulin response, 2nd phase insulin response, and insulin sensitivity index.

.0434) and 2ndIR ($r^2 = .0276$). Plasma insulin concentration at 90 minutes solely depended on ISI ($P < .0001$), which affected 30.77% of the variation of plasma insulin concentration at 90 minutes. Univariate analysis showed that ISI accounted for 38.14% of the variation in plasma insulin concentration at 120 minutes. Multivariate analysis confirmed the univariate analysis and found that 40.87% of its variation could be explained by ISI and gender.

DISCUSSION

The goal of this study is to investigate the relative contributions of insulin sensitivity and β-cell function on plasma insulin concentrations during the OGTT. Because hypertension is associated with insulin resistance and because hyperglycemia affects both insulin sensitivity and β-cell function, we only investigated normotensive and glucose-tolerant subjects. Our results showed that insulin sensitivity plays a key role on plasma insulin concentrations at fasting, 60, 90, and 120 minutes with very little influence from β-cell function (1stIR and 2ndIR). In contrast, 1stIR plays a key role on the determination of postchallenged plasma insulin concentration at 30 minutes, while ISI and 2ndIR had no impact on it. The measures during the OGTT provided substantial information about insulin sensitivity, but very limited information about β-cell function. Because the majority of the variation in plasma glucose and insulin concentrations cannot be explained by the covariate analyzed in this study (as shown in Tables 2 and 3), these results suggest that other factors (such as free fatty acid, leptin, glucagon-like peptide 1, etc) could also affect these measures.

It is well recognized that a 2-hour postchallenged plasma glucose concentration has a higher sensitivity (up to 97%) for the diagnosis of diabetes than the fasting plasma glucose concentration.[19-21] Postchallenged hyperglycemia persists for several years before fasting hyperglycemia occurs.[22] In addition, postchallenged plasma glucose concentrations have been shown to be a better marker for glycemic control in diabetic patients.[23] The 2-hour postprandial plasma glucose concentration accounts for 25% of the variation in glycosylated hemoglobin,[24] the level of which is closely related to the prevalence of diabetic retinopathy, nephropathy, and neuropathy.[25] Furthermore, postchallenged glucose concentration has been shown to be an independent risk factor for atherosclerosis, not only in patients with NIDDM, but also in nondiabetic subjects.[26,27] Therefore, it is important to understand how postchallenged (or postprandial) hyperglycemia develops. NIDDM is the result of an imbalance between insulin sensitivity and β-cell function. Postchallenged hyperglycemia could be the result of insulin resistance, beta cell dysfunction, or the combination of both. The relative importance of insulin sensitivity and β-cell function on postchallenged plasma glucose concentration has not been examined systematically. Our results indicate that postchallenged plasma glucose concentrations at 60, 90, and 120 minutes increase as insulin resistance worsens. Although we did not study subjects with impaired glucose tolerance, our observations suggest that increasing insulin resistance plays an important role on the conversion from glucose tolerance to impaired glucose tolerance. As insulin sensitivity decreases, plasma glucose concentration would increase and eventually exceed the normal range, resulting in impaired glucose tolerance. This extrapolation of our observation to impaired glucose-tolerant subjects is consistent with the notion from the Pima Indians study that insulin resistance is the main determinant for the transition from normal to impaired glucose tolerance.[28]

Plasma glucose and insulin concentrations have been shown to be inherited quantitative traits.[11,29,30] In addition, numerous loci have been found to be linked to plasma insulin concentrations in humans[31-33] and in rodents.[34] However, it is not clear what these linkages mean in relation to insulin resistance and β-cell dysfunction, which are the key metabolic defects in NIDDM. Our data showed that, at most, 19% of the variation in plasma glucose concentration could be explained by ISI and, at most, 17% to 32% of the variation in plasma insulin concentration can be explained by either ISI or 1stIR. Therefore, the chance of detecting a genetic locus, which affects either insulin sensitivity or β-cell function, is not great if plasma glucose or insulin concentrations are used as phenotypic traits. This was clearly demonstrated in the genetic studies of the Otsuka Long-Evans Tokushima Fatty (OLEFT) rats, in which the cholecystokinin type A receptor (CCKAR) gene was interrupted,[35] leading to poor regeneration of the pancreas after a subtotal pancreatectomy as the cause of β-cell dysfunction. This locus was barely detected when one used plasma glucose concentrations as the phenotypic traits.[36-41]

The drastic difference in the prevalence of NIDDM has been thought to be caused by a genetic influence. We previously showed that there was a difference in insulin sensitivity among 4 ethnic groups.[17] To further compare the utility of insulin sensitivity and β-cell function with the utility of plasma glucose and insulin concentrations, we compared the influence of ethnicity on plasma glucose and insulin concentrations compared with insulin sensitivity and β-cell function. As shown in Table 4, the present study included 28 Asian Americans, 11 African Americans, 46 Caucasian Americans, and 20 Mexican Americans. During the hyperglycemic clamps, no difference was noted in the steady-state plasma glucose concentrations. The coefficient of variation for steady-state plasma glucose levels was 5.2% ± 0.5% for Asian Americans; 5.9% ± 1.0% for African Americans; 5.8% ± 0.3% for Caucasian Americans; and 5.1% ± 0.5% for Mexican Americans. Significant differences were noted in ISI, G_{Cl}, 1stIR, and 2ndIR among the 4 ethnic groups. No differences were noted in plasma glucose or insulin concentrations during the OGTT, except for marginal differences among the 4 ethnic groups in plasma insulin concentrations at 60 and 120 minutes, which were mainly affected by ISI (33.52% and 38.14%, respectively). These observations indicate that it is very unlikely to detect the factors that mainly affect β-cell function if one only examines plasma glucose or insulin concentrations, while the power to detect the factor affecting insulin sensitivity is also compromised.

In summary, our results indicate that plasma insulin concentrations are mainly determined by insulin sensitivity, not β-cell function, except for the plasma insulin concentration at 30 minutes, 24.09% of which depends on 1stIR. Therefore, if one only uses plasma insulin concentrations as the phenotypic traits

Table 4. Clinical Features, Insulin Sensitivity, and β-Cell Function by Ethnicity

	Asian Americans	African Americans	Caucasian Americans	Mexican Americans	*P*
No.	28	11	46	20	
OGTT					
Fasting plasma glucose (mmol/L)	4.66 (4.54, 4.78)	4.63 (4.25, 5.00)	4.72 (4.62, 4.82)	4.60 (4.39, 4.81)	NS
Plasma glucose at 30 min (mmol/L)	7.67 (7.31, 8.04)	7.13 (6.37, 7.88)	7.41 (7.02, 7.80)	7.03 (6.57, 7.48)	NS
Plasma glucose at 60 min (mmol/L)	7.40 (6.96, 7.84)	7.22 (6.51, 7.94)	7.06 (6.62, 7.50)	6.98 (6.40, 7.57)	NS
Plasma glucose at 90 min (mmol/L)	6.61 (6.12, 7.11)	6.42 (5.48, 7.37)	6.23 (5.82, 6.65)	6.26 (5.77, 6.75)	NS
Plasma glucose at 120 min (mmol/L)	6.03 (5.64, 6.43)	6.43 (5.87, 6.99)	5.64 (5.33, 5.95)	5.89 (5.38, 6.40)	NS
Fasting plasma insulin* (mmol/L)	4.12 (4.01, 4.22)	4.12 (3.84, 4.33)	4.13 (4.04, 4.21)	4.26 (4.10, 4.40)	NS
Plasma insulin at 30 min* (mmol/L)	6.29 (5.96, 6.54)	6.12 (5.70, 6.41)	5.87 (5.69, 6.03)	6.15 (5.80, 6.41)	NS
Plasma insulin at 60 min* (mmol/L)	6.14 (5.90, 6.33)	6.01 (5.66, 6.26)	5.81 (5.68, 5.93)	6.10 (5.81, 6.32)	.046
Plasma insulin at 90 min* (mmol/L)	5.88 (5.59, 6.10)	5.87 (5.41, 6.18)	5.60 (5.43, 5.74)	5.86 (5.62, 6.05)	NS
Plasma insulin at 120 min* (mmol/L)	5.70 (5.46, 5.89)	5.81 (5.30, 6.15)	5.45 (5.28, 5.59)	5.87 (5.58, 6.09)	.018
Hyperglycemic clamp					
Steady-state plasma glucose (mmol/L)	10.06 (9.93, 10.19)	9.84 (9.59, 10.09)	10.05 (9.95, 10.15)	10.02 (9.87, 10.17)	NS
ISI* ($\mu M/m^2/min/pmol/L$)	4.03 (3.22, 5.04)	5.06 (3.29, 7.76)	6.76 (5.83, 7.83)	4.20 (3.16, 5.60)	<.001
Glucose clearance* ($L/m^2/min/pmol$)	0.411 (0.328, 0.514)	0.514 (0.335, 0.789)	0.673 (0.582, 0.779)	0.420 (0.316, 0.558)	<.001
1st IR* (pmol/L)	1,980 (1,498, 2,617)	1,744 (1,218, 2,496)	1,320 (1,137, 1,533)	1,986 (1,690, 2,335)	.006
2nd IR* (pmol/L)	569 (463, 698)	494 (339, 718)	343 (296, 397)	533 (431, 659)	<.001

NOTE. Mean (95% CI) or n (%).
Abbreviation: NS, not significant.
*Geometric mean (95% CI).

in the genetic study of NIDDM without the measurement of β-cell function, only very limited information will be gained on β-cell function from the study. Our observations imply that it is essential to measure β-cell function in vivo if one plans to study the genetic influence of β-cell dysfunction in NIDDM. In contrast, plasma insulin concentrations at various time points are good surrogates for insulin sensitivity. Substantial information on insulin sensitivity will be revealed from studies using plasma insulin concentrations as the phenotypic traits for insulin sensitivity. Proper phenotyping, especially the assessment of β-cell function, is an important endeavor in the genetic study of NIDDM.

ACKNOWLEDGMENT

We thank Mohammed F. Saad, MD, for the measurement of plasma insulin concentration and the staff of the General Clinical Research Center at the University of California, Los Angeles for their continued support. We also thank Audrey Chu, George P. Tsai, Jennifer M. Ryu, Jennifer L. McGullam, and Jennifer E. McCarthy for their laboratory assistance.

REFERENCES

1. Chiu KC, Province MA, Permutt MA: Glucokinase gene is genetic marker for NIDDM in American blacks. Diabetes 41:843-849, 1992

2. King H, Rewers M: Global estimates for prevalence of diabetes mellitus and impaired glucose tolerance in adults. WHO Ad Hoc Diabetes Reporting Group. Diabetes Care 16:157-177, 1993

3. Japan Diabetes Society: Diabetes mellitus in twins: A cooperative study in Japan. Committee on Diabetic Twins, Japan Diabetes Society. Diabetes Res Clin Pract 5:271-280, 1988

4. Lo SS, Tun RY, Hawa M, et al: Studies of diabetic twins. Diabetes Metab Rev 7:223-238, 1991

5. Newman B, Selby JV, King MC, et al: Concordance for type 2 (non-insulin-dependent) diabetes mellitus in male twins. Diabetologia 30:763-768, 1987

6. Medici F, Hawa M, Ianari A, et al: Concordance rate for type II diabetes mellitus in monozygotic twins: Actuarial analysis. Diabetologia 42:146-150, 1999

7. Knowler WC, Pettitt DJ, Saad MF, et al: Diabetes mellitus in the Pima Indians: Incidence, risk factors and pathogenesis. Diabetes Metab Rev 6:1-27, 1990

8. Martin BC, Warram JH, Rosner B, et al: Familial clustering of insulin sensitivity. Diabetes 41:850-854, 1992

9. Elbein SC, Hasstedt SJ, Wegner K, et al: Heritability of pancreatic beta-cell function among nondiabetic members of Caucasian fa-

milial type 2 diabetic kindreds. J Clin Endocrinol Metab 84:1398-1403, 1999

10. Sakul H, Pratley R, Cardon L, et al: Familiality of physical and metabolic characteristics that predict the development of non-insulin-dependent diabetes mellitus in Pima Indians. Am J Hum Genet 60:651-656, 1997

11. Watanabe RM, Valle T, Hauser ER, et al: Familiarity of quantitative metabolic traits in Finnish families with non-insulin-dependent diabetes mellitus. Finland-United States Investigation of NIDDM Genetics (FUSION) Study investigators. Hum Hered 49:159-168, 1999

12. Pimenta W, Korytkowski M, Mitrakou A, et al: Pancreatic beta-cell dysfunction as the primary genetic lesion in NIDDM. Evidence from studies in normal glucose-tolerant individuals with a first-degree NIDDM relative. JAMA 273:1855-1861, 1995

13. DeFronzo RA, Bonadonna RC, Ferrannini E: Pathogenesis of NIDDM. A balanced overview. Diabetes Care 15:318-368, 1992

14. Ferrannini E, Natali A, Capaldo B, et al: Insulin resistance, hyperinsulinemia, and blood pressure: Role of age and obesity. European Group for the Study of Insulin Resistance (EGIR). Hypertension 30:1144-1149, 1997

15. Ferrannini E, Buzzigoli G, Bonadonna R, et al: Insulin resistance in essential hypertension. N Engl J Med 317:350-357, 1987

16. Rossetti L, Giaccari A, DeFronzo RA: Glucose toxicity. Diabetes Care 13:610-630, 1990

17. Chiu KC, Cohan P, Lee NP, et al: Insulin sensitivity differs among ethnic groups with a compensatory response in beta-cell function. Diabetes Care 23:1353-1358, 2000

18. DeFronzo RA, Tobin JD, Andres R: Glucose clamp technique: A method for quantifying insulin secretion and resistance. Am J Physiol 237:E214-E223, 1979

19. de Vegt F, Dekker JM, Stehouwer CD, et al: The 1997 American Diabetes Association criteria versus the 1985 World Health Organization criteria for the diagnosis of abnormal glucose tolerance: Poor agreement in the Hoorn Study. Diabetes Care 21:1686-1690, 1998

20. Harris MI: Undiagnosed NIDDM: Clinical and public health issues. Diabetes Care 16:642-652, 1993

21. Puavilai G, Chanprasertyotin S, Sriphrapradaeng A: Diagnostic criteria for diabetes mellitus and other categories of glucose intolerance: 1997 criteria by the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus (ADA), 1998 WHO consultation criteria, and 1985 WHO criteria. World Health Organization. Diabetes Res Clin Pract 44:21-26, 1999

22. Harris MI, Klein R, Welborn TA, et al: Onset of NIDDM occurs at least 4-7 yr before clinical diagnosis. Diabetes Care 15:815-819, 1992

23. de Veciana M, Major CA, Morgan MA, et al: Postprandial versus preprandial blood glucose monitoring in women with gestational diabetes mellitus requiring insulin therapy. N Engl J Med 333:1237-1241, 1995

24. Soonthornpun S, Rattarasarn C, Leelawattana R, et al: Postprandial plasma glucose: A good index of glycemic control in type 2 diabetic patients having near-normal fasting glucose levels. Diabetes Res Clin Pract 46:23-27, 1999

25. UKPDS: Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. Lancet 352:837-853, 1998

26. Donahue RP, Abbott RD, Reed DM, et al: Postchallenge glucose concentration and coronary heart disease in men of Japanese ancestry. Honolulu Heart Program. Diabetes 36:689-692, 1987

27. Lowe LP, Liu K, Greenland P, et al: Diabetes, asymptomatic hyperglycemia, and 22-year mortality in black and white men. The Chicago Heart Association Detection Project in Industry Study. Diabetes Care 20:163-169, 1997

28. Saad MF, Knowler WC, Pettitt DJ, et al: A two-step model for development of non-insulin-dependent diabetes. Am J Med 90:229-235, 1991

29. Mitchell BD, Kammerer CM, Hixson JE, et al: Evidence for a major gene affecting postchallenge insulin levels in Mexican-Americans. Diabetes 44:284-289, 1995

30. Hsueh WC, Wagner MJ, Mitchell BD, et al: Diabetes in the Old Order Amish — Characterization and heritability analysis of the Amish Family Diabetes Study. Diabetes Care 23:595-601, 2000

31. Pratley RE, Thompson DB, Prochazka M, et al: An autosomal genomic scan for loci linked to prediabetic phenotypes in Pima Indians. J Clin Invest 101:1757-1764, 1998

32. Mitchell BD, Kammerer CM, O'Connell P, et al: Evidence for linkage of postchallenge insulin levels with intestinal fatty acid-binding protein (FABP2) in Mexican-Americans. Diabetes 44:1046-1053, 1995

33. Mitchell BD, Cole SA, Hsueh WC, et al: Linkage of serum insulin concentrations to chromosome 3p in Mexican Americans. Diabetes 49:513-516, 2000

34. Kido Y, Philippe N, Schaffer AA, et al: Genetic modifiers of the insulin resistance phenotype in mice. Diabetes 49:589-596, 2000

35. Nakamura H, Kihara Y, Tashiro M, et al: Defects of cholecystokinin (CCK)-A receptor gene expression and CCK-A receptor-mediated biological functions in Otsuka Long-Evans Tokushima Fatty (OLETF) rats. J Gastroenterol 33:702-709, 1998

36. Watanabe TK, Okuno S, Oga K, et al: Genetic dissection of "OLETF," a rat model for non-insulin-dependent diabetes mellitus: Quantitative trait locus analysis of (OLETF x BN) x OLETF. Genomics 58:233-239, 1999

37. Moralejo DH, Ogino T, Zhu M, et al: Identification of a quantitative trait locus influencing plasma insulin levels after 70% pancreatectomy using the OLETF rat. J Vet Med Sci 60:1157-1160, 1998

38. Kanemoto N, Hishigaki H, Miyakita A, et al: Genetic dissection of "OLETF", a rat model for non-insulin-dependent diabetes mellitus. Mamm Genome 9:419-425, 1998

39. Nara Y, Gao M, Ikeda K, et al: Genetic analysis of non-insulin-dependent diabetes mellitus in the Otsuka Long-Evans Tokushima Fatty rat. Biochem Biophys Res Commun 241:200-204, 1997

40. Sugiura K, Miyake T, Taniguchi Y, et al: Identification of novel non-insulin-dependent diabetes mellitus susceptibility loci in the Otsuka Long-Evans Tokushima fatty rat by MQM-mapping method. Mamm Genome 10:1126-1131, 1999

41. Wei S, Wei K, Moralejo DH, et al: Mapping and characterization of quantitative trait loci for non-insulin-dependent diabetes mellitus with an improved genetic map in the Otsuka Long-Evans Tokushima fatty rat. Mamm Genome 10:249-258, 1999