Earlier Appearance of Impaired Insulin Secretion Than of Visceral Adiposity in the Pathogenesis of NIDDM

5-Year Follow-Up of Initially Nondiabetic Japanese-American Men

KWANG-WEN CHEN, MD
EDWARD J. BOYKO, MD
RICHARD W. BERGSTROM, MD
DONNA L. LEONETTI, PHD
LAURA NEWELL-MORRIS, PHD
PATRICIA W. WAHL, PHD
WILFRED Y. FUJIMOTO, MD

OBJECTIVE — To identify risk factors for development of non-insulin-dependent diabetes mellitus (NIDDM) during a 5-year longitudinal follow-up of second-generation Japanese-American (Nisei) men.

RESEARCH DESIGN AND METHODS — For 5 years, 137 initially nondiabetic Nisei men were followed with 75-g oral glucose tolerance tests at the initial visit and at 2.5- and 5-year follow-up visits. Body fat distribution was assessed by computed tomography (CT) and body mass index (BMI) calculated at each visit. Fasting insulin and C-peptide, the increment of insulin and C-peptide at 30 min after the oral glucose load, intra-abdominal and total subcutaneous fat by CT, and BMI were compared between those who remained nondiabetic (non-DM) and those who had developed NIDDM at 2.5 years (DM-A) and 5 years (DM-B).

RESULTS — At baseline, the DM-A group had significantly increased intra-abdominal fat, elevated fasting plasma C-peptide, and lower C-peptide response at 30 min after oral glucose. At the 2.5-year follow-up, this group had markedly increased fasting plasma insulin and decreased 30-min insulin and C-peptide response to oral glucose. The DM-B group also had significantly lower insulin response at 30 min after oral glucose at baseline but no significant difference in intra-abdominal fat or fasting plasma insulin and C-peptide levels. When this group developed NIDDM by 5-year follow-up, however, an increase of intra-abdominal fat was found superimposed on the pre-existing lower insulin response. Fasting plasma insulin and C-peptide remained low.

CONCLUSION — In DM-A, lower 30-min insulin response to oral glucose (an indicator of β-cell lesion) and increased intra-abdominal fat and fasting C-peptide (indicators of insulin resistance) were the risk factors related to the development of NIDDM. DM-B subjects had a lower 30-min insulin response to oral glucose at baseline and increased intra-abdominal fat at 5 years, when they were found to have NIDDM. Thus, both insulin resistance and impaired β-cell function contribute to the development of NIDDM in Japanese-Americans, and impaired β-cell function may be present earlier than visceral adiposity in some who subsequently develop NIDDM.

From the Departments of Medicine (K.W.C., E.J.B., R.W.B., W.Y.F.), Anthropology (D.L.L., L.N.-M.), and Biostatistics (P.W.W.), University of Washington, Seattle, Washington.

Address correspondence and reprint requests to Wilfred Y. Fujimoto, MD, Department of Medicine RG-26, University of Washington School of Medicine, Seattle, WA 98195.

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BMI, body mass index; IGT, impaired glucose tolerance; ICR, incremental C-peptide response; IGR, incremental glucose response; IIR, incremental insulin response; NGT, normal glucose tolerance; NIDDM, non-insulin-dependent diabetes mellitus; OGTT, oral glucose tolerance test; OR, odds ratio; RICR, relative ICR; RIIR, relative IIR.

Numerous studies have shown that both insulin resistance and impaired insulin secretion occur in non-insulin-dependent diabetes mellitus (NIDDM) (1–3). The temporal sequence of insulin resistance and impaired insulin secretion is controversial (4–16). Insulin resistance, which may be compensated for by hyperinsulinemia, was proposed as the primary abnormality by Reaven (1). Insulin resistance is often accompanied by central obesity, dyslipidemia, hypertension, and atherosclerosis, a combination that has been called the insulin resistance syndrome, metabolic syndrome, or syndrome X. DeFronzo et al. (2) have also stated that NIDDM is largely due to insulin resistance and in only some NIDDM patients is impairment of insulin secretion the initial lesion. On the other hand, Porte (3) reviewed NIDDM as a heterogeneous disorder in which islet dysfunction plays a critical role while insulin resistance contributes to producing the final syndrome. Mitrakou et al. (4) concluded that late hyperinsulinemia after ingestion of glucose may be the consequence of an inadequate early β-cell response rather than of insulin resistance. Efendic and Östenson (5) have proposed that defective insulin response to glucose is a prerequisite for the development of NIDDM. In the Japanese-American Community Diabetes Study, we have shown an association of elevated fasting C-peptide and intra-abdominal fat distribution and lower 30-min C-peptide response to oral glucose at baseline with the development of NIDDM at a 2.5-year follow-up of initially nondiabetic second-generation (Nisei) Japanese-American men (17,18).

We have now completed 5-year follow-up studies of 137 initially nondiabetic Nisei men and report an additional 10 cases of patients who had developed NIDDM at 5 years and had baseline characteristics that differed from those found in the earlier group. We describe these differences and their significance below.

RESEARCH DESIGN AND METHODS— The 137 subjects were recruited from 229 second-generation Japanese-American men (American-born and -reared sons of immigrants from Japan) who were enrolled in the Japanese-American Community Diabetes Study. Details pertaining to the recruitment, enrollment, characterization, and generation assignment of the study sample have been reported previously (19). The protocol for this research was reviewed and approved by the Human Subjects Review Committee at the University of Washington. Written consent was obtained from each subject.

Subjects were initially classified with normal glucose tolerance (NGT), impaired glucose tolerance (IGT), or NIDDM based on information obtained from the subjects and their physicians and results of a 75-g oral glucose tolerance test (OGTT), interpreted by World Health Organization criteria (20). Seventy-seven subjects had NGT, 74 had IGT, and 78 had NIDDM at baseline. After 5 years, 137 nondiabetic men (71 NGT, 66 IGT) participated in the follow-up examination, which included an OGTT. Fourteen men (4 in the first and 10 in the last 2.5 years) were not re-examined because they had died (2 NGT, 1 IGT), were ill (1 NGT, 4 IGT), no longer resided in the area (1 NGT, 1 IGT), or declined re-examination (2 NGT, 2 IGT).

The following procedures were performed at the initial visit and at the 2.5- and 5-year follow-up visits. Age (years and months), height (m), and weight (kg) were recorded, and body mass index (BMI) was calculated (kg/m^2). At 0800, after a 10-h fast, blood samples were drawn before and at 30, 60, 90, 120, and 180 min after a 75-g oral glucose load (Glucola, Hopping Bottle, Sunnyvale, CA). Fasting plasma glucose, insulin, and C-peptide levels and the response of these three variables over 3 h to oral glucose were measured at each of the five time points. Glucose was measured by an automated glucose oxidase method (Department of Laboratory Medicine, University of Washington Medical Center). Plasma insulin and C-peptide were measured by radioimmunoassay performed in the Radioimmunoassay Core of the Diabetes Endocrinology Research Center. The intra- and interassay coefficients of variation were 5 and 8% for insulin and 7 and 11% for C-peptide, respectively.

The incremental insulin response (IIR) and incremental C-peptide response (ICR) at 30 min were calculated by subtracting the fasting values from the plasma levels at 30 min. Relative IIR (RIIR) and relative ICR (RICR) were calculated by dividing the IIR and the ICR by the fasting plasma level of that peptide. The IIR, ICR, and incremental glucose response (IGR) at 30 min were used to calculate the IIR:IGR and ICR:IGR ratios. These variables were used to assess β-cell response to oral glucose.

Cross-sectional body fat areas (cm^2) were determined by computed tomography (CT) at four sites (subcutaneous thorax, subcutaneous abdomen, subcutaneous thigh, and intra-abdomen) as previously described (19). The subcutaneous fat areas were summed to give an estimate of total nonvisceral fat.

Data were analyzed with the Statistical Package for Social Sciences (21). Differences among groups were analyzed with one-way analysis of variance test. Pairwise comparisons were tested by Tukey's studentized range test. All values are expressed as means ± SE. Assumptions made when using ratios were verified by using analysis of covariance. Logistic regressions analysis with NIDDM existence at 2.5- or 5-year follow-up was performed for selected baseline risk variables, and odds ratios (ORs) with 95% confidence intervals were calculated for a 20% difference in the value of continuous variables, calculated from the range of values observed for these variables in the entire study sample.

RESULTS— We have previously reported 15 cases who had developed NIDDM at 2.5-year follow-up (17,18), of whom 13 (DM-A) have now been followed for 5 years. Another 10 cases (DM-B) had developed NIDDM at 5-year follow-up, and 114 subjects (non-DM) remained nondiabetic. The variables are shown and compared among these three groups.

The mean baseline ages were 62.7 ± 1.6, 63.9 ± 1.7, and 60.7 ± 0.5 years in the DM-A, DM-B, and non-DM groups, respectively ($P = 0.15$).

Fasting plasma glucose and status of glucose tolerance

When compared with non-DM, fasting plasma glucose levels were significantly higher in DM-A and DM-B at baseline, 2.5 years, and 5 years (Table 1). In the DM-A group, 11 had IGT and 2 NGT at baseline; at 5 years, 3 still had NIDDM, 7 had returned to IGT, and 3 had improved to NGT. In the DM-B group, nine had IGT and one had NGT at baseline; one of those with IGT had improved to NGT at 2.5 years, while the others still had IGT. In the non-DM group, 68 had NGT and 46 IGT at baseline, 75 had NGT and 39 had IGT at 2.5 years, and 65 had NGT and 49 had IGT at 5 years.

Fasting insulin and C-peptide

When compared with non-DM, baseline fasting C-peptide levels were significantly different, DM-A being significantly higher (Table 1). Fasting insulin levels were not significantly different among the three groups. At the 2.5-year follow-up examination, fasting insulin had risen in DM-A such that both fasting insulin and C-peptide levels were significantly higher in this group than in the other two groups. At the 5-year follow-up, neither fasting insulin nor C-peptide levels were significantly different among the groups.

Insulin and C-peptide responses at 30 min

At baseline, IIR, RIIR, and IIR:IGR were significantly different among the groups (Table 1). In particular, DM-B had significantly lower insulin response than non-DM. RICR was significantly lower in DM-A than non-DM, while DM-B had

Table 1—*Fasting insulin and C-peptide and insulin and C-peptide response to oral glucose at baseline and 2.5- and 5-year follow-up*

	Group			
	DM-A	DM-B	Non-DM	*P* value
n	13	10	114	—
Baseline				
Fasting glucose	6.10 ± 0.21*	6.05 ± 0.11*	5.59 ± 0.05	0.0003
Fasting insulin (pmol/l)	78 ± 8	64 ± 11	65 ± 3	0.27
Fasting C-peptide (nmol/l)	1.21 ± 0.09*	1.01 ± 0.08	0.86 ± 0.03	0.0003
IIR (pmol/l)	277 ± 42	235 ± 69*	392 ± 27	0.0084
ICR (nmol/l)	0.93 ± 0.10	0.84 ± 0.25	1.02 ± 0.04	0.46
RIIR	3.7 ± 0.4	4.0 ± 1.3	6.7 ± 0.6	0.0059
RICR	0.82 ± 0.11*	0.92 ± 0.26	1.24 ± 0.05	0.011
IIR (pmol/l):IGR (mmol/l)	61 ± 8	57 ± 18*	105 ± 7	0.001
ICR (nmol/):IGR (mmol/l)	0.21 ± 0.02	0.21 ± 0.06	0.29 ± 0.02	0.30
2.5-year follow-up				
Fasting glucose	6.19 ± 0.20*	5.97 ± 0.18*	5.27 ± 0.05	<0.0001
Fasting insulin (pmol/l)	137 ± 23†	77 ± 14	95 ± 4	0.014
Fasting C-peptide (nmol/l)	1.19 ± 0.07†	0.93 ± 0.06	0.94 ± 0.02	0.0015
IIR (pmol/l)	262 ± 60*	270 ± 59	451 ± 32	0.0064
ICR (nmol/l)	0.34 ± 0.08*	0.51 ± 0.22	0.82 ± 0.04	0.0001
RIIR	2.0 ± 0.3*	4.8 ± 2.0	5.3 ± 0.4	0.0003
RICR	0.28 ± 0.06*	0.63 ± 0.32	0.92 ± 0.05	0.0001
IIR (pmol/l):IGR (mmol/l)	67 ± 13*	44 ± 8*	113 ± 11	0.004
ICR (nmol/l):IGR (mmol/l)	0.09 ± 0.03*	0.07 ± 0.03*	0.21 ± 0.02	<0.001
5-year follow-up				
Fasting plasma glucose	5.85 ± 0.19*	6.29 ± 0.24*	5.34 ± 0.05	<0.0001
Fasting insulin (pmol/l)	120 ± 12	87 ± 12	101 ± 4	0.15
Fasting C-peptide (nmol/l)	0.96 ± 0.08	0.78 ± 0.09	0.79 ± 0.03	0.17
IIR (pmol/l)	343 ± 73	277 ± 70	479 ± 37	0.036
ICR (nmol/l)	0.84 ± 0.09	0.72 ± 0.13	1.05 ± 0.05	0.10
RIIR	2.7 ± 0.4	3.9 ± 1.4	6.2 ± 1.3	0.060
RICR	0.95 ± 0.11	0.99 ± 0.23	1.48 ± 0.11	0.085
IIR (pmol/l):IGR (mmol/l)	81 ± 14	65 ± 16*	148 ± 19	0.015
ICR (nmol/l):IGR (mmol/l)	0.20 ± 0.02	0.18 ± 0.04*	0.31 ± 0.03	0.046

Data are means ± SE. Fasting insulin, IIR, and RIIR were computed on logarithms. RICR was computed on square roots. IIR:IGR was computed for IIR adjusted for IGR and ICR:IGR was computed for ICR adjusted for IGR by analysis of covariance. * Significantly different from non-DM by Tukey's studentized range test. † Significantly different from DM-B and non-DM by Tukey's studentized range test.

nonsignificantly lower RICR than non-DM. ICR was not significantly different among the groups. At 2.5-year follow-up, when DM-A had developed diabetes, IIR, RIIR, ICR, and RICR were all significantly lower in DM-A than in non-DM. In addition, both IIR:IGR and ICR:IGR were significantly lower in DM-A and DM-B than in non-DM. At 5-year follow-up, DM-B tended to have the lowest insulin and C-peptide responses, both IIR:IGR and ICR:IGR being significantly lower than in non-DM.

Fat deposition and BMI

At baseline, intra-abdominal fat was significantly different among the groups, DM-A having significantly greater intra-abdominal fat than non-DM (Table 2). Differences in both BMI and total subcutaneous fat, however, were not significant. At 2.5 and 5 years, differences in intra-abdominal fat were again significantly different among the groups and DM-A had significantly more intra-abdominal fat than non-DM. Differences in BMI and total subcutaneous fat were not significant at 2.5 and 5 years. Although DM-B had the lowest intra-abdominal fat, subcutaneous fat, and BMI at baseline, at 5 years it showed increases of both intra-abdominal and subcutaneous fat. The increase in intra-abdominal fat was borderline significant by paired Student's *t* test ($P = 0.076$).

Risk of developing NIDDM by logistic regression analysis

The risk of developing NIDDM by 2.5- or 5-year follow-up in relation to base-

Table 2—*Intra-abdominal and total subcutaneous fat measured by CT and BMI at baseline and 2.5- and 5-year follow-up*

	Group			
	DM-A	DM-B	Non-DM	*P* value
n	13	10	114	—
Baseline				
Intra-abdominal fat (cm^2)	147 ± 16*	103 ± 22	110 ± 5	0.048
Total subcutaneous fat (cm^2)	307 ± 24	270 ± 44	321 ± 11	0.77
BMI (kg/m^2)	26.3 ± 0.9	24.6 ± 1.2	25.4 ± 0.3	0.38
2.5-year follow-up				
Intra-abdominal fat (cm^2)	154 ± 19*	108 ± 16	117 ± 5	0.035
Total subcutaneous fat (cm^2)	317 ± 25	325 ± 51	327 ± 11	0.96
BMI (kg/m^2)	25.8 ± 0.8	24.4 ± 1.3	25.3 ± 0.3	0.49
5-year follow-up				
Intra-abdominal fat (cm^2)	157 ± 18*	140 ± 22	115 ± 4	0.0086
Total subcutaneous fat (cm^2)	315 ± 26	336 ± 46	330 ± 13	0.92
BMI (kg/m^2)	26.2 ± 0.8	24.7 ± 1.2	25.4 ± 0.3	0.54

Data are means ± SE. * Significantly different from non-DM by Tukey's studentized range test.

line measures was estimated by logistic regression analysis (Table 3). ORs were calculated for a 20% difference in these baseline measures. For example, a 20% higher baseline fasting C-peptide level was associated with a 2.3-fold increase in the odds of developing NIDDM over the follow-up period. This analysis demonstrated that fasting plasma glucose, IIR, RIIR, IIR:IGR, fasting C-peptide, and RICR were significantly related to the odds of developing NIDDM. Higher IIR, RIIR, IIR:ICR, and RICR were related to lower NIDDM odds, while higher fasting plasma glucose and fasting C-peptide were related to higher NIDDM odds.

CONCLUSIONS— We have reported that Nisei Japanese-American men in King County, Washington, had a higher prevalence of NIDDM than native men in Japan and that factors associated with migration might account for this (19,22). Furthermore, subjects with IGT or NIDDM had lower oral glucose–stimulated insulin response and more intra-abdominal fat than those with NGT (18,23). We originally reported 15 cases who developed NIDDM after 2.5 years of follow-up who had at baseline signifi-

Table 3—*Logistic regression analysis of NIDDM occurrence by 2.5- or 5-year follow-up in relation to baseline measures, with OR (95% confidence intervals) calculated for a 20% change in baseline values of the risk variable (calculated from the range of values observed for the risk variable in the entire study sample)*

Independent variable	Range	*P* value	OR (95% confidence interval)
Fasting plasma glucose (mmol/l)	3.9–7.7	0.0004	3.80 (1.79–8.08)
Fasting insulin (pmol/l)	6–198	0.22	1.34 (0.78–2.29)
IIR (pmol/l)	24–1,572	0.043	0.40 (0.16–0.99)
RIIR	0.29–57.5	0.0016	0.029 (0.002–0.41)
IIR:IGR (pmol/l:mmol/l)	8.9–428.6	0.0027	0.28 (0.10–0.83)
Fasting C-peptide (nmol/l)	0.3–1.9	0.0008	2.30 (1.40–3.78)
ICR	−0.03–2.7	0.24	0.71 (0.39–1.28)
RICR	−0.03–4.0	0.0031	0.26 (0.10–0.65)
ICR:IGR	−0.01–1.03	0.11	0.61 (0.32–1.17)
Intra-abdominal fat (cm^2)	0.7–254.8	0.15	1.37 (0.88–2.14)
BMI (kg/m^2)	18.9–36.9	0.84	1.06 (0.60–1.86)
Total subcutaneous fat (cm^2)	22.1–1,053.1	0.48	0.73 (0.31–1.75)

$n = 23$. Fasting insulin, IIR, and RIIR were computed on logarithms. IIR:IGR was computed for IIR adjusted for IGR, ICR:IGR for ICR adjusted for IGR, and BMI for weight adjusted for height squared.

cantly more intra-abdominal fat, higher fasting C-peptide, and relatively lower 30-min insulin response after oral glucose (17,18). Both increased fasting C-peptide level and intra-abdominal fat are related to insulin resistance (24–26). Therefore, insulin resistance and impaired insulin secretion appeared to play roles in the pathogenesis of NIDDM in Nisei men. However, the temporal sequence of insulin resistance and the insulin secretion defect remained uncertain.

Thus, it is interesting that men who had developed diabetes at a 5-year follow-up had significantly lower insulin response to oral glucose without any increase of fasting insulin or intra-abdominal fat at baseline. This finding suggests that the defect in insulin secretion may precede the appearance of insulin resistance and visceral adiposity. Several other studies have come to the similar conclusion that an insulin secretion defect may precede the development of NIDDM (4–9). An insulin secretion defect has also been reported in first-degree relatives of NIDDM patients who did not have insulin resistance (10).

Other cross-sectional and longitudinal studies have supported insulin resistance as the primary lesion and have found no evidence of impaired insulin secretion (11–16). Because these studies used fasting insulin (11), first-phase insulin secretion in response to intravenous glucose (12–14), and 2-h post–oral glucose load insulin concentration (15,16) to assess insulin secretion, differences in methodology assessing different components of insulin secretion, such as capacity, sensitivity to glucose, or kinetics of insulin release, may explain differing results (27). It is clear, however, that the 30-min insulin secretion response to oral glucose is reduced in subjects who developed NIDDM in this study as well as a study of native Japanese by Kadowaki et al. (6). The ratio of the 30-min increment in insulin concentration to the 30-min increment in glucose concentration (IIR: IGR), reported to be a good measure of glucose-stimulated insulin secretion (28), was also shown to be significantly low at baseline, 2.5, and 5 years in DM-B compared with non-DM and a risk factor for development of NIDDM by logistic regression analysis.

Groop et al. (27) have suggested that many other factors, such as heterogeneity of NIDDM, ethnic differences, obesity, and age, can account for differences attributed to the relative importance of insulin resistance or insulin deficiency as the primary lesion of NIDDM. Nonobese diabetic patients are usually reported to have lower insulin secretion (2,5). Aging is another cause of diminished insulin secretion (29,30). In this study, the subjects were older and nonobese by BMI even when diabetic, which may partially explain their lower insulin responses. Another study in a population of Japanese by Kadowaki et al. (6) also showed lower insulin response before development of NIDDM. This observation and ours suggest that this impairment of insulin secretion may be ethnically related. Whether β-cell dysfunction in NIDDM is hereditary or acquired, however, is still unknown.

Increased intra-abdominal fat at baseline is another significant risk factor for the development of NIDDM in the DM-A group and more important than BMI or total subcutaneous fat, as shown in this report. In DM-B, the substantial increment of intra-abdominal fat at 5 years may have played an important role additional to the pre-existing lower insulin response. Visceral adiposity may be associated with increased products of lipolysis (free fatty acids and glycerol) and stimulate hepatic glucose production (31,32), which could account for its association with insulin resistance and abnormalities of glucose tolerance. Increased intra-abdominal fat is related to age, male gender, and physical inactivity, but the mechanisms underlying its development remain inconclusive (33).

Both the DM-A group, which had developed NIDDM at 2.5 years, and the DM-B group, which had developed NIDDM at 5 years, had a high proportion of individuals with IGT at baseline and higher fasting plasma glucose at all time points. IGT and the fasting glucose level are established risk factors for the development of NIDDM (34,35), which is reconfirmed in this study. Fasting plasma glucose as well as IIR, RIIR, IIR:IGR, fasting C-peptide, and RICR were shown to be significant risk factors in logistic regression analysis. However, intra-abdominal fat and fasting insulin were not significant risk factors for the development of NIDDM by this analysis. This is probably due to the differences between men who developed diabetes by 2.5-year follow-up and those who developed it by 5-year follow-up in the relationship of visceral adiposity and insulin resistance to the development of NIDDM, and it is consistent with heterogeneity with respect to these factors in the pathogenesis of NIDDM. We also note that there are some discrepancies between the fasting and post-stimulation C-peptide and insulin observations in terms of their statistical significance when comparing among the groups. One possible explanation is the effect of hepatic insulin extraction upon plasma insulin levels, which may be different between groups and during follow-up. During follow-up, both fasting and glucose-stimulated C-peptide tended to decrease and insulin to increase. These changes cause a decrease in the C-peptide:insulin ratio that may be partly explained by decreased hepatic insulin extraction (36). Both aging and obesity have been reported to be associated with decreased hepatic insulin extraction (37, 38).

In summary, heterogeneity in the relationship of risk factors to the development of NIDDM was observed. In a group of men with earlier onset (by 2.5-year follow-up) of NIDDM, higher intra-abdominal fat and fasting C-peptide and relatively lower 30-min insulin response to oral glucose were observed at baseline. In a second group of men with later onset (by 5-year follow-up) of NIDDM, lower insulin response to oral glucose and intra-abdominal fat were observed at baseline;

when NIDDM had developed by 5-year follow-up, intra-abdominal fat was found to have increased. We suggest that both insulin resistance and impaired insulin secretion contribute to the development of NIDDM in Japanese-Americans and impaired insulin secretion may be present earlier than increased visceral adiposity in some who subsequently develop NIDDM. Since visceral adiposity is correlated with insulin resistance, we conclude that a β-cell lesion is present, probably coexists with insulin resistance, and may even antedate insulin resistance in some of these men and that NIDDM developed after the β-cell could no longer accommodate to the additional demand imposed by insulin resistance upon insulin secretion.

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