

Risk Factors for the Development of NIDDM in Yonchon County, Korea

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OBJECTIVE — To determine the risk factors for the development of NIDDM in Yonchon County of Korea.

RESEARCH DESIGN AND METHODS — We studied 1,193 Korean nondiabetic subjects at baseline who participated in a 2-year follow-up study on diabetes in Yonchon County. A 75-g oral glucose tolerance test was performed 2 years after the baseline examination. Age, sex, and anthropometric and metabolic characteristics at baseline were analyzed simultaneously as potential predictors of conversion to NIDDM. We also designed a nested case-control study to determine the role of hyperinsulinemia and/or hyperproinsulinemia in the conversion to NIDDM in patients with newly developed diabetes and control subjects matched for age, sex, BMI, and waist-to-hip-ratio.

RESULTS — At 2 years, 67 subjects developed diabetes, as defined by World Health Organization criteria. The age-adjusted incidence was significantly higher in men (6.4%) than in women (3.0%), and the incidence increased as age increased in both sexes. Multiple logistic regression analysis revealed age, male sex, and fasting and 2-h glucose levels to be significant risk factors for the development of NIDDM, whereas waist-to-hip ratio and BMI were not. In a nested case-control study, baseline proinsulin but not insulin levels were significantly higher in subjects who progressed to NIDDM than in those who did not.

CONCLUSIONS — In the Korean population, β -cell dysfunction, as measured by high proinsulin levels, seems to be associated with subsequent development of NIDDM, whereas regional and general obesity and fasting insulin levels, which may be a surrogate for insulin resistance, were not.

In recent decades, NIDDM has become a major public health problem in Korea (1,2). In 1993, in a community-based cross-sectional study, we reported that the prevalence of diabetes in Yonchon County, Korea, was 7.2% in the population over age 30 years. This figure was much higher than previously suggested, and even higher than in many Western countries. In addition to the higher prevalence, the natural history of diabetes in Korea seems to be quite different from that observed in Western coun-

tries. Most of the NIDDM patients in Korea are not obese, and many of them lose weight significantly during the course of developing diabetes (3). Moreover, insulin sensitivity in first-degree relatives of Korean NIDDM patients was not lower than that in the control subjects (4). Therefore, insulin deficiency rather than insulin resistance has been suggested as the major pathogenic mechanism of most Korean NIDDM patients. In the Yonchon study (1), we identified central obesity, serum triglyc-

eride levels, age, systolic blood pressure, family history, and living in urban areas as factors significantly associated with diabetes (1). However, there has been no prospective study to determine the risk factors associated with the development of NIDDM in Korea.

Various markers have been reported so far as predictors of the development of NIDDM. High fasting insulin and C-peptide levels have been shown to predict deterioration to NIDDM in a number of populations in whom insulin resistance plays a major role in the development of diabetes (5–9). However, in other studies, parameters of β -cell dysfunction, such as high fasting proinsulin levels (10,11) and high proinsulin-to-insulin ratio (12,13), were found to be predictive for the conversion to diabetes.

In this study, we followed the initially nondiabetic cohort of the Yonchon study to determine the risk factors that can predict the development of NIDDM in the Korean population.

RESEARCH DESIGN AND METHODS

Subjects

This study consisted of two parts: one a prospective cohort study and the other a nested case-control study. The target cohort of this study was 2,293 subjects living in Yonchon County who participated in the baseline examination in 1993 but were free of diabetes. The initial study was a population-based cross-sectional study of diabetes conducted in February 1993. Subjects age ≥ 30 years were randomly selected from the registry of Yonchon County. Among the 3,804 residents selected, 2,520 subjects participated, giving an overall participation rate of 66%. Details of the method of recruiting the study subjects and the procedures for the baseline examination have been published previously (1).

At the baseline examination, anthropometric measurements (height, weight, and waist and hip circumference) were made in a standard manner. BMI was calculated as weight in kilograms divided by height in meters squared, and waist-to-hip ratio (WHR) as waist circumference divided by

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Received for publication 5 April 1997 and accepted in revised form 6 August 1997.

Abbreviations: OGTT, oral glucose tolerance test; WHR, waist-to-hip ratio.

Table 1—Respondents and nonrespondents by age and sex

Age (years)	Respondents		Nonrespondents		Total	
	Men	Women	Men	Women	Men	Women
30–39	74	110	113	160	187	270
40–49	114	155	97	119	211	274
50–59	151	209	94	134	245	343
60–69	108	142	71	117	179	259
≥70	69	78	62	71	131	149
Subtotal	516	694	437	601	953	1,295
Total (%)	1,210 (53.8)		1,038 (46.3)		2,248 (100)	

Data are n. Seventeen subjects were interviewed but not venipunctured, so complete data were analyzed for 1,193 subjects.

hip circumference. Blood specimens were obtained after a 12- to 14-h fast for determination of plasma glucose, cholesterol, triglyceride, and serum insulin concentrations. All subjects underwent a 75-g oral glucose tolerance test (OGTT). Diabetes was defined according to World Health Organization (WHO) criteria. Subjects were defined as having hypertension if their systolic blood pressure was ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg, or if they were receiving drug treatment for hypertension (14).

Study design

In February 1995, a 2-year follow-up study of the 1993 cohort was performed. The target cohort of this study was the 2,293 people judged to be free of diabetes at the baseline examination. To identify new cases, this target cohort was invited to visit centers in their respective neighborhoods for examination. Subsequent to the baseline examination, 29 subjects died and 16 moved out of Yonchon County, leaving 2,248 subjects eligible for the follow-up study, of whom 1,210 subjects participated (Table 1). Of these, 17 subjects were interviewed but not venipunctured, so complete data were available for analysis in 1,193 subjects. At baseline, 1,040 had normal glucose tolerance and 153 subjects had impaired glucose tolerance. All subjects underwent 75-g OGTT. Diabetes was defined according to WHO criteria; patients who had begun treatment with insulin or oral hypoglycemic agents after the initial examination were also defined as diabetic.

We also designed a nested case-control study to determine the role of baseline hyperinsulinemia and/or hyperproinsulinemia in the development of NIDDM. As a case group, we selected those who converted to diabetes in 2 years, and also picked up the same number of subjects, as

a control group, from the 1,126 nonconverters whose age, sex, BMI, and WHR matched those of the converters. We measured baseline proinsulin and insulin levels of these two groups.

Plasma glucose was determined by the glucose oxidase method. Plasma insulin was determined by a commercial solid-phase radioimmunoassay (Diagnostic Products, Los Angeles, CA). Plasma proinsulin was measured by a double antibody radioimmunoassay (lot UV 207; Linco Research, St. Louis, MO), in which insulin and 64,65 split proinsulin cross-reacts by less than 0.1%. In this assay des 31,32 proinsulin cross-reacts by 95%.

Statistical analyses

Means are presented with 95% CIs. Fasting insulin concentrations were log transformed to improve their skewed distribution. The antilogs of the insulin levels are reported in the tables. For the risk factor analysis, age-adjusted group means for baseline characteristics were computed by analysis of covariance (Table 3) with PC-SAS package. For the univariate analysis, the Mantel-Haenszel χ^2 test was used to test the association of the various risk factors with conversion to NIDDM. Multiple logistic regression analysis was used to estimate the odds ratio associated with each risk factor via the EGRET system. WHR was divided into tertiles and treated as a categorical variable. Age and sex were entered first in the regression equation as potential confounders. Subsequently, the other independent variables with the best fit were entered stepwise into the equation.

RESULTS— In 2 years, 67 new cases of diabetes developed in this cohort (Table 2). Of these 67 new cases, 47 had had normal glucose tolerance and 20 had had impaired

Table 2—A 2-year incidence of NIDDM in Yonchon County by age and sex

Age (years)	Men	Women
30–39	2/71 (2.8)	2/107 (1.9)
40–49	7/113 (6.2)	6/154 (3.9)
50–59	12/149 (8.1)	1/207 (0.5)
60–69	10/107 (9.3)	8/140 (5.7)
≥70	13/68 (19.1)	6/77 (7.8)
Subtotal	44/508 (8.7)	23/685 (3.4)
Total	67/1,193 (5.6)	

Data are n (%).

glucose tolerance at baseline. We compared the baseline characteristics of subjects who converted to NIDDM with those who remained free of diabetes (Table 3). Subjects who converted to diabetes were older and more likely to be male, and had higher fasting and 2-h postload glucose and triglyceride levels.

When we performed univariate analysis, the incidence increased as the age of the subjects increased in both sexes (χ^2 trend = 10.8, $P < 0.01$ in men; χ^2 trend = 4.7, $P < 0.05$ in women). We also found that the incidence of diabetes increased as baseline WHR increased in men (χ^2 trend = 7.2, $P < 0.01$), whereas such a tendency was not found in women (χ^2 trend = 1.1, $P > 0.05$). Both systolic (χ^2 trend = 10.3, $P < 0.01$) and diastolic (χ^2 trend = 6.0, $P < 0.05$) blood pressure elevation at baseline was also related to the development of diabetes. Subjects with higher fasting (χ^2 trend = 18.0, $P < 0.001$) and 2-h postload (χ^2 trend = 24.7, $P < 0.001$) plasma glucose concentrations at baseline were more likely to develop diabetes.

When the development of NIDDM was examined as a binary outcome by using logistic regression analysis while simultaneously adjusting for all other risk factors, age, male sex, and higher fasting and postload plasma glucose levels were significantly associated with an increased odds of developing NIDDM, whereas fasting insulin levels, WHR, and BMI had no statistical significance (Table 4).

In the nested case-control study, although the baseline insulin levels were 9.3% higher in subjects who progressed to NIDDM than those who did not (46.9 [CI 42.5–51.2] vs. 42.9 [CI 39.9–45.9] pmol/l, respectively), this difference was not significant. In contrast, baseline fasting proinsulin levels were significantly higher in subjects who progressed compared with those who

Table 3—Age-adjusted baseline characteristics of nonconverters and converters to NIDDM

	Converters	Nonconverters	P value
n	67	1,126	
Sex (% M/F)	66/34 (44/23)	41/59 (464/662)	<0.001
Age (years)	59.6 (56.5–62.7)	53.5 (52.8–54.2)	<0.001
BMI (kg/m ²)	24.5 (23.5–25.3)	24.2 (24.0–24.3)	0.332
WHR*	0.88 (0.88–0.91)	0.87 (0.86–0.87)	0.740
Fasting plasma glucose (mmol/l)	6.09 (5.94–6.29)	5.59 (5.56–5.62)	<0.001
2-h plasma glucose (mmol/l)	6.71 (6.44–7.23)	5.93 (5.83–6.01)	<0.001
Fasting insulin (pmol/l)	46.9 (42.5–51.2)	44.3 (42.8–45.8)	0.432
Triglycerides (mmol/l)	1.98 (1.67–2.38)	1.67 (1.60–1.74)	0.048
Total cholesterol (mmol/l)	4.05 (3.89–4.34)	4.09 (4.05–4.15)	0.696
HDL cholesterol (mmol/l)	0.91 (0.85–0.99)	0.97 (0.95–0.99)	0.106
sBP (mmHg)	130 (128–139)	125 (124–129)	0.055
dBp (mmHg)	84 (81–89)	81 (80–85)	0.139
Family history of diabetes (%)	6.0	5.3	0.958

Data are arithmetic means (95% CI), except for insulin, which is logarithmically transformed and presented as geometric means (95% CI). For fasting insulin, statistical tests were computed on logarithmic transformation. Comparison of the sex ratio and family history was performed by χ^2 test. *WHR was adjusted for both age and sex.

did not (16.0 [CI 12.4–19.7] vs. 8.7 [CI 7.4–10.1] pmol/l; $P < 0.001$) (Table 5).

CONCLUSIONS— In this community-based cohort study, we have found that age, male sex, and fasting and postload plasma glucose levels are significant risk factors for the incidence of NIDDM. The results of a nested case-control study also suggest that fasting proinsulin levels could be a predictor for the development of NIDDM in Koreans.

The response rate in this study was only 53.8%, so that a response bias is possible. Moreover, the response rate in younger subjects was much lower than that in older subjects. Because the incidence of diabetes was higher in older subjects, the consequences of this selection may be an overestimation of incidence. Thus the actual incidence in this study is assumed to be slightly lower when the untested segment of population is stratified by age. However, there was no significant difference in other variables, such as family history of diabetes, fasting and postload plasma glucose levels, BMI, and WHR at baseline between the subjects who participated in the follow-up examination and those who did not (data not shown). Therefore, it is suggested that our results on the relation between risk factors and the development of NIDDM might have not been seriously affected by the low response rate.

It is well known that there is a subset of diabetic patients who initially present as NIDDM but progress eventually to IDDM

(15). Because we did not evaluate the immunogenetic characteristics or C-peptide responses of the converters, it is quite possible that some of the patients may belong to the so-called slowly progressive IDDM group. However, considering the fact that the incidence of IDDM in Korea is very low (16), and actual prevalence of the slowly progressive IDDM in Korean adult diabetic patients is also very low (17), we can cautiously assume that there are few, if any, IDDM patients included in the converters. It should be also noted that the prevalence of anti-GAD antibodies and HLA-DQA1 and DQB1 susceptibility alleles was very low among the newly diagnosed diabetic patients of the initial cross-sectional study (18).

BMI was not a significant predictor of diabetes in either sex, and WHR was significantly related to diabetes only in men (although that association lost significance after adjustment for other variables). These results are somewhat different from those of other epidemiological studies and the documented significance of WHR in the initial cross-sectional study (1). The reason for this difference is unclear at present, but may be due to the small number of women who converted to diabetes. The other possibility may be the etiologic difference of NIDDM in Koreans when compared with Caucasians. Although obesity has been most consistently associated with an increased risk of NIDDM in many ethnic groups, such strong associations were obtained from cross-sectional studies of international comparisons. It became clear from several cross-sectional studies reported in the last decade that not all the variation in the prevalence of NIDDM can be explained by either the frequency or degree of obesity (19,20). Moreover, prospective studies that have related degree of obesity to subsequent incidence of NIDDM have revealed that the relation, although positive, was not linear, with a modest increase in incidence over a wide range of BMIs or relative weight and subsequent increases in very obese individuals (21–24). Because the majority of our cohort is not obese, with only 60 subjects (5%) with BMI >30, it may not have been possible for the trend analysis to demonstrate any association between BMI and the risk for NIDDM.

In this study, we found no association of baseline fasting insulin levels with the

Table 4—Multivariate logistic regression analysis of 2-year incidence of NIDDM

	Odds ratio	95% CI	P value
Age (10-year difference)	1.49	1.16–1.92	0.0020
Sex (M/F)	2.65	1.42–4.93	0.0021
Fasting plasma glucose (1 mmol/l difference)	2.73	1.75–4.26	<0.0001
2-h plasma glucose (1 mmol/l difference)	1.22	1.03–1.45	0.0204
Fasting insulin (1 natural log difference)	1.57	0.83–3.01	0.1658
Hypertension (yes/no)	1.21	0.69–2.13	0.5135
BMI (5 kg/m ² difference)	0.96	0.63–1.46	0.8356
WHR			
<0.84	1	—	—
0.85–0.89	1.59	0.66–3.84	0.2198
>0.89	0.95	0.49–1.84	0.2987

Relative odds were estimated using logistic regression analysis. Hypertension was defined if systolic blood pressure was ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg or if subjects were receiving drug treatment for hypertension.

Table 5—Baseline fasting insulin and proinsulin concentrations in those who converted to NIDDM and their age, sex, BMI, and WHR-matched control subjects who remained nondiabetic after 2 years

	Remained nondiabetic	Converted to NIDDM	P value
n	66	67	—
Sex (M/F)	44/22	44/23	—
Age (years)	59.5 (56.4–62.6)	59.6 (56.5–62.7)	0.959
BMI (kg/m ²)	24.0 (23.3–24.8)	24.4 (23.5–25.3)	0.536
WHR	0.89 (0.88–0.90)	0.90 (0.88–0.91)	0.682
Fasting insulin (pmol/l)	42.9 (39.9–45.9)	46.9 (42.5–51.2)	0.134
Fasting proinsulin (pmol/l)	8.7 (7.4–10.1)	16.0 (12.4–19.7)	<0.001

Data are arithmetic means (95% CI), except for logarithmically transformed data, which are presented as geometric means (95% CI). For fasting insulin and proinsulin, statistical tests were computed on logarithmic transformation.

development of NIDDM. Baseline fasting insulin levels also showed no difference between converters and nonconverters in the nested case-control study. Elevated serum insulin concentrations have been shown to predict deterioration to NIDDM in a number of populations with high risk for NIDDM (5). These results were demonstrated in the Nauruans (6), Pimas (7), Mexican-Americans (8), and Australian Aborigines (9), in whom insulin resistance plays a major role in the development of diabetes. Concerning the relative importance of insulin resistance or insulin deficiency as the primary lesion of NIDDM, Groop et al. (25) suggested that ethnic differences, obesity, and age can determine the differences. Chen et al. (26), in their study on Japanese-Americans, suggested that impaired β -cell function may be present earlier than insulin resistance in those who subsequently develop NIDDM. Another study in a population of Japanese by Kadawaki et al. (27) also showed lower insulin response before development of NIDDM. Because Korean people are genetically very close to Japanese people and in the midst of similar rapid environmental change, it is possible that similar mechanisms may be involved in the pathogenesis of diabetes in Korea. Moreover, we found that fasting proinsulin levels were significantly higher in converters than in nonconverters matched for age, sex, BMI, and WHR. Similar results were observed in Japanese-Americans (28) and in Danish studies (29). Because high fasting proinsulin levels have been used as a measure of β -cell dysfunction (10,11), we suggest that β -cell dysfunction as assessed by proinsulin levels seems to be associated with subsequent development of NIDDM, whereas fasting insulin levels, which may be a surrogate for

insulin resistance, are not associated in the Korean population.

The greater incidence in men than in women found in this study was surprising. Higher prevalence of diabetes in men was also found in Japanese-Americans (30), Singaporeans (31), and Taiwanese <50 years old (32). However, a previous cross-sectional study did not find any sex difference in the prevalence of diabetes in this area. The reason for this sex difference is not certain, and we are trying to determine the basis for it.

In summary, we have demonstrated that age, male sex, and mild fasting and postprandial hyperglycemia as well as hyperproinsulinemia could predict the later development of NIDDM in Koreans. The results of our study suggest that β -cell dysfunction, rather than insulin resistance, may play an important role in the future development of NIDDM.

Acknowledgments— This work was supported by Korean Science and Engineering Foundation Grant 93-0800-08-01-3.

We thank Dr. Wilfred Y. Fujimoto at the University of Washington and Dr. Ki-Up Lee at the University of Ulsan for their helpful criticism during the preparation of this manuscript, and Dr. Dong Hyun Kim at the Hallym University College of Medicine for his consultation on the statistical analyses. We are indebted to Drs. Won Bae Kim, Tae Geun Oh, Seok In Lee, Hyun Kyu Kim, Young Ho Kang, all the public health physicians in the Yonchon County, Ms. Jung Ye Lee, RN, and Ms. Jung-Ja Lee, RN for their dedicated help in the studies. We thank the personnel of the Yonchon Health Center and graduate school students of Seoul National University Department of Food and Nutrition for their full cooperation. Finally, we are grateful to the men and women of Yonchon County who participated in the study.

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