Obesity as a Risk Factor for Non-insulin-dependent Diabetes Mellitus in Korea

Most Korean patients with non-insulin-dependent diabetes mellitus (NIDDM) have been reported not to be obese, and many of them lost weight significantly during the course of their disease. In this regard, a retrospective cohort study was conducted to determine the relationship between body mass index (BMI, kg/m^2) and the risk for NIDDM among Koreans. Subjects who had received a medical examination from 1990 to 1991 and who were available for the detection of NIDDM until September 1999 were included. Subjects who initially had diabetes or were diagnosed as diabetic within 1 yr after enrollment were excluded. We reviewed the medical records of final cohort of 2,531 subjects. Follow-up of this cohort revealed 117 cases with diabetes with an incident of 7.8 per 1,000 person-years. Compared with those with BMI less than 23 kg/m^2, the adjusted relative risks for diabetes mellitus for those with BMI of 23-24.9, 25-26.9, and greater than 27 kg/m^2 were 0.85 (0.47-1.50), 1.29 (0.72-2.31), and 3.38 (1.22-4.63), respectively, for men (p for trend < 0.01) and as for 9.14 (1.99-41.8), 7.36 (1.47-36.8), and 14.5 (3.03-69.2), respectively, for women (p for trend < 0.01). These data indicate a direct relationship between obesity and the risk for the development of diabetes, emphasizing the importance of weight control for the prevention of NIDDM in Koreans.

Key Words : *Diabetes Mellitus, Non-Insulin-Dependent; Obesity; Body Mass Index; Risk Factors*

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INTRODUCTION

During the last decades, the prevalence of non-insulin-dependent diabetes mellitus (NIDDM) increased worldwide, and the disease has become one of the major public health problems in Korea (1, 2). NIDDM affects about 7.2% of Korean adults over 30 yr of age (3, 4). Harboring a genetic background, the prevalence steadily increases with advancing ages. Other risk factors include obesity and a previous history of gestational diabetes or impaired glucose tolerance. Diet, exercise, and weight reduction have been implicated for the reduction of the risk for diabetes (5). Natural history of diabetes in Korea seems to be quite different from that observed in western countries (6). Most Korean patients with NIDDM have been reported not to be obese, and many of them lost weight significantly during the course of their disease (7, 8). Most of all, the association between diabetes and obesity is unclear in Koreans. In cross-sectional studies, the patients with diabetes were more obese than the control groups (9-11). However, a prospective cohort study over a 2-yr follow-up period showed that obesity was not a risk factor for the development of NIDDM (12).

In this regard, we conducted a retrospective cohort study to investigate obesity as a risk factor for NIDDM among Korean adults.

MATERIALS AND METHODS

Study subjects

Initial cohort was established in 1991 and is for an ongoing study on the risk factors for chronic diseases, including hypertension and diabetes in Seoul, Korea. At Asan Medical Center in Seoul, 4,287 adults aged 17 to 80 yr received medical examination from June 1990 to February 1991. We reviewed their medical records from January 1998 to October 1999. Subjects without follow-up visit or with the final visit within 1 yr from the baseline medical examination were excluded. We defined the remaining 2,674 subjects as the Asan cohort.

For this study, we excluded 73 subjects who had had diabetes at baseline medical examination, and 7 subjects in whom diabetes had developed within 1 yr from the baseline medical examination. Another 63 subjects whose medical

record lacked the relevant information were also excluded. We further defined the remaining 2,531 subjects as the Asan diabetes cohort. The selection process is illustrated in Fig. 1.

Baseline Measurements

The baseline medical examination consisted of medical history, physical examination, anthropometric measurements, and a health risk appraisal questionnaire (e.g. daily cigarette and alcohol consumption, physical activity level, family history of chronic disease, and past medical history). Anthropometric parameters, including height and weight, were measured with the subjects wearing light clothing without shoes. The body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared (kg/m^2). After overnight fasting, all participants were subject to laboratory examinations including fasting glucose and HbA1c.

Diagnosis of NIDDM

Two physicians reviewed the medical records of the Asan cohort to reveal the incidence of NIDDM from January 1998 to September 1999. Incident diabetes was defined by a report of pharmacologically treated diabetes at least 1 yr after the baseline medical examination or a physician's diagnosis of diabetes in hospital records. We considered subject with fasting glucose less than 110 mg/dL as free of diabetes
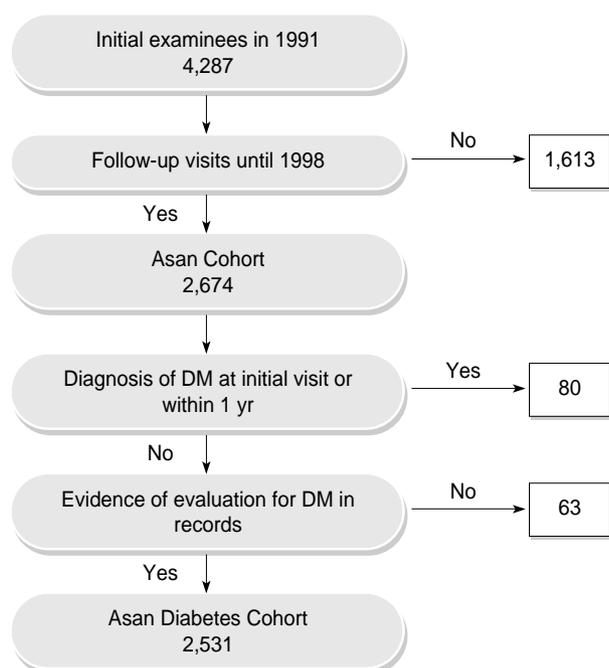
and subject with fasting glucose 110-140 mg/dL, who was excluded from final cohort, as an indeterminate case. None of the incident cases had features suggestive of insulin-dependent diabetes mellitus such as a history of ketosis or immediate need for insulin therapy at diagnosis. The earliest date of diagnosis of diabetes available in medical records was defined as the event date.

Table 1. Baseline characteristics among a cohort of 1,551 men and 980 women*

	Men (n=1,551)	Women (n=980)
Age (yr)		
< 40	331 (21.3)	347 (35.4)
40-49	787 (50.7)	354 (36.2)
50-59	316 (20.4)	218 (22.2)
≥60	117 (7.6)	61 (6.2)
Marital status		
unmarried	41 (2.8)	25 (2.8)
married	1,406 (95.8)	827 (91.4)
single	20 (1.4)	53 (5.8)
Education		
middle school	110 (7.5)	186 (20.8)
high school	423 (28.7)	378 (42.2)
college	803 (54.5)	303 (33.8)
postgraduate course	136 (9.3)	29 (3.2)
Occupation		
professional	389 (27.2)	79 (9.4)
administration	85 (5.9)	7 (0.8)
office worker	358 (25.1)	52 (6.2)
sales	161 (11.3)	49 (5.8)
service	120 (8.4)	43 (5.1)
agriculture	130 (9.1)	76 (9.0)
manufacture	46 (3.2)	12 (1.4)
others	139 (9.8)	523 (62.3)
Family history of diabetes		
absent	1,258 (83.2)	745 (80.9)
present	42 (16.8)	176 (19.1)
Smoking history		
non-smoker	307 (20.3)	667 (76.9)
ex-smoker	376 (24.8)	39 (4.5)
current smoker	832 (54.9)	162 (18.6)
Alcohol consumption		
non-drinker	200 (13.2)	496 (56.4)
ex-drinker	61 (4.0)	31 (3.5)
current drinker	1,259 (82.8)	352 (40.1)
Frequency of taking regular exercise		
< 1/week	669 (47.1)	397 (48.5)
1-2/week	372 (26.2)	170 (20.8)
≥3/week	379 (26.7)	251 (30.7)
Body mass index (kg/m^2)		
< 20.0	452 (29.1)	377 (38.5)
20.0-22.9	146 (9.4)	177 (18.1)
23.0-24.9	516 (33.3)	212 (21.6)
25.0-26.9	311 (20.1)	124 (12.6)
≥27.0	126 (8.1)	90 (9.2)
mean±SD	23.5±2.6	22.7±3.0

Values represent the number of subjects (%), unless indicated. *missing values were excluded

Fig. 1. Selection of study subjects.

Table 2. Crude incidence rate and relative risk for NIDDM among a cohort of 1,551 men and 980 women

Characteristics	Men					Women				
	person-years	new cases of NIDDM	crude incidence*	relative risk[†]	95% confidence interval	person-years	new cases of NIDDM	crude incidence*	relative risk[†]	95% confidence interval
Age (yr)										
< 40	1,960	7	3.6	1.0		2,069	4	1.9	1.0	
40-49	4,614	36	7.8	2.24	0.99-5.04	2,142	10	4.7	2.22	0.69-7.09
50-59	1,847	26	14.1	3.89	1.69-9.97	1,358	10	7.4	3.28	1.02-10.49
≥60	697	17	24.4	6.59	2.73-15.89	374	7	18.7	8.19	2.38-28.10
					p for trend <0.001					p for trend <0.001
Body mass index (kg/m²)										
< 23.0	3,456	24	6.9	1.0		3,321	2	0.9	1.0	
23.0-24.9	3,050	24	7.9	1.11	0.63-1.96	1,260	12	9.5	14.83	3.32-66.32
25.0-26.9	1,888	24	12.7	1.76	0.98-3.09	786	8	10.2	14.34	3.04-67.68
≥27.0	724	14	19.3	2.79	1.44-5.39	576	9	15.6	23.42	5.06-108.48
					p for trend <0.001					p for trend <0.001
Family history of diabetes										
Absent	7,240	52	7.2	1.0		4,323	22	5.1	1.0	
Present	1,474	33	22.3	2.94	1.90-4.55	1,158	7	6.0	0.94	0.40-2.21
Frequency of taking regular exercise										
< 1 /week	3,827	36	9.4	1.0		2,393	13	5.4	1.0	
1-2 /week	2,223	21	9.4	0.98	0.58-1.64	1,071	5	4.7	0.67	0.25-1.77
≥3 /week	2,247	20	8.9	0.90	0.53-1.52	1,415	4	2.8	0.48	0.17-1.40
Total smoking amount (pack-years)										
None	1,829	14	7.7	1.0		4,139	17	4.1	1.0	
< 30	5,224	48	9.2	1.38	0.76-2.50	775	7	9.0	2.52	1.06-6.01
≥30	1,861	24	12.9	1.97	1.02-3.80	394	5	12.7	4.18	1.54-11.38
					p for trend=0.025					p for trend <0.001
Alcohol consumption (g/day)										
None	1,259	17	13.5	1.0						
< 10	3,741	27	7.2	0.64	0.35-1.17	3,178	14	4.4	1.0	
10-30	2,232	26	11.6	1.00	0.54-1.85	1,715	12	6.9	1.68	0.80-3.53
≥30	1,723	16	9.3	0.78	0.39-1.55	518	2	3.8	0.86	0.19-3.72
Education										
Middle school	681	8	11.8	1.0		1,143	11	9.6	1.0	
High school	2,434	28	11.5	1.21	0.62-2.37	2,281	12	5.3	0.63	0.27-1.37
College or postgraduate	5,506	46	8.4	0.89	0.48-1.69	2,014	5	2.5	0.30	0.11-0.85
										p for trend=0.025

*incidence per 1,000 person-years; [†]generated from Cox proportional hazards model

Statistical analysis

Subjects were initially classified according to their BMI into five groups: 'thin' (BMI<20.0 kg/m²), 'ideal' (BMI 20.0-22.9 kg/m²), 'borderline' (BMI 23.0-24.9 kg/m²), 'overweight' (BMI 25.0-26.9 kg/m²), and 'obese' (BMI ≥ 27.0 kg/m²). However, the number of incident cases of 'thin' group was too small for analysis and thus we combined the 'thin' and 'ideal' groups. Cox proportional hazards model was used to assess the independent contributions of the individual risk factors to the subsequent NIDDM, and to obtain relative risks adjusted for other risk factors. The assumption of proportionality underlying these regression models was confirmed by examining log-log plots. All tests of significance were two-tailed.

RESULTS

The general characteristics of the subjects are shown in Table 1. The mean age was 45.9 yr (range, 17 to 80) for men and 44.3 yr (range, 17 to 75) for women. After a mean follow-up period of 5.95 yr, there were 117 new cases of NIDDM among the 2,531 subjects. The annual incidence was calculated as 7.8 per 1,000 person-yr of follow-up (9.4 in men and 5.2 in women).

Table 2 shows the estimated incidence rates of NIDDM according to variables, which, for men, increased with advancing age, BMI, and greater than 30 pack-years of smoking. For women, advancing age, BMI, greater than 30 pack-years of smoking, and increasing educational level were associated with increasing estimated incidence of NIDDM. Family history of diabetes was a significant risk

Table 3. Adjusted relative risk and 95% confidence interval for NIDDM among a cohort of 1,551 men and 980 women

Risk Factors	Men			Women		
	Relative Risk	95% confidence interval	*p*-value*	Relative Risk	95% confidence interval	*p*-value*
Age (5 yr increase)	1.35	1.21–1.49	0.001	1.29	1.17–1.43	0.016
Family history of diabetes						
Absent	1.0			1.0		
Present	3.02	1.93–4.73	0.001	0.84	0.35–2.05	0.703
Total smoking amount (pack-years)						
None	1.0			1.0		
< 30	1.59	0.87–2.91	0.129	3.21	1.28–8.29	0.013
≥ 30	2.09	1.08–4.63	0.029	3.91	11.24–12.35	0.020
			p for trend=0.018			*p* for trend=0.015
Body mass index (kg/m²)						
< 23.0	1.0			1.0		
23.0 – 24.9	0.85	0.47–1.50	0.569	9.14	1.99–41.8	0.004
25.0 – 26.9	1.29	0.72–2.31	0.395	7.36	1.47–36.8	0.015
≥ 27.0	3.38	1.22–4.63	0.010	14.5	3.03–69.2	0.001
			p for trend=0.005			*p* for trend=0.005
Education						
Middle school	1.0			1.0		
High school	1.45	0.71–2.94	0.304	0.65	0.26–1.60	0.347
College or postgraduate	0.93	0.48–1.81	0.839	0.35	0.11–1.10	0.073
						p for trend=0.150

*Using Cox proportional hazards model. All risk factors above are used as covariates

factor for developing NIDDM in men, but not in women.

Table 3 shows the relative risks of NIDDM at different ranges of BMI, adjusted for age, more than 30 pack-years of smoking, and a family history of diabetes in men, and educational levels for women. Compared with men having BMI less than 23 kg/m², the adjusted relative risks for diabetes mellitus for men with BMI 23-24.9, 25-26.9 kg/m², and greater than 27 kg/m² were 0.85 (95% CI, 0.47-1.50), 1.29 (0.72-2.31), and 3.38 (1.22-4.63), respectively. For men, age, more than 30 pack-years of smoking, and a family history of diabetes were risk factors for NIDDM. Compared with women having BMI less than 23 kg/m², the adjusted relative risks for diabetes mellitus in women with BMI 23-24.9, 25-26.9, and greater than 27 kg/m² were 9.14 (1.99-4.18), 7.36 (1.47-36.8), and 14.5 (3.03-69.2), respectively. As for women, age and more than 30 pack-years of smoking were risk factors for NIDDM. Educational level lost its significance when adjusted for other risk factors.

DISCUSSION

In this retrospective cohort study, we observed a strong positive relationship between BMI and the risk for NIDDM in Korean adults. Risk increased with BMI greater than 23 kg/m² after adjusting for other risk factors. Age, total smoking amount over 30 pack-years, and a family history of diabetes were significant predictors of risk for NIDDM in men. Age and total smoking amount were significant pre-

dictors of risk for NIDDM in women.

We chose 2,531 study subjects from 4,287 baseline subjects. To rule out selection bias from this process, we reviewed the basic characteristics of follow-up and non-follow-up group. The follow-up group has more men than non-follow-up group. Except difference from sex, the baseline BMI between two groups did not show any statistical differences. This may lead to biased incidence rate of NIDDM in these study subjects compared with Korean population. But our study question is not to identify the incidence of NIDDM in Korea but to identify the obesity is a risk factor to developing NIDDM. As we analyzed data separately, the sex difference would not affect on the risk evaluation between obesity and diabetes.

Studies with a wide range of populations including Scandinavians (13), South Pacific Islanders (14), Pima Indians (15), and Mexican Americans (16) have shown an association between obesity and diabetes. Even though the natural history of NIDDM in Koreans seems to be quite different from those in other ethnic groups (6), we identified similar associations in Korean adults.

Although BMI was the main predictor of risk for NIDDM, the effect of BMI on NIDDM was different in men and women, with a greater risk for women than men, especially those with a lower BMI. Women with a normal weight were at increased risk compared with women having BMI less than 23 kg/m². Our results showed similarities to those of the Nurses' Health Study (17). They followed up 113,861 females in the United States for 8 yr, and documented that even with an average weight, women

were at increased risk for clinical NIDDM and that the relationship between BMI and risk for diabetes was continuous.

The longitudinal design of this study greatly reduced the probability of biased reporting of weight and avoided the problem of weight change following the diagnosis of diabetes, which might be a serious problem in case-control studies. Accuracy of diagnosis of NIDDM was ensured by requiring two physicians to agree on the diagnosis based on data in medical records. It is still controversial whether cigarette smoking is a risk factor for the development of NIDDM (18-21). Our study showed an association between cigarette smoking and risk of diabetes. For men, the smoking history over 30 pack-years was a strong predictor of diabetes. For women, the risk of diabetes increased with the amount of smoking.

Family history of diabetes was a predictor of risk for NIDDM in men, but not in women. The role of heredity in the etiology of NIDDM is well established (22, 23). We asked study subjects about their family history of diabetes in siblings or parents. Because the number of women who developed NIDDM was small, the data might have been insufficient to reveal a true association between NIDDM and family history of diabetes.

Physical activity was not associated with risk for NIDDM in this study. Increased physical activity was effective in preventing NIDDM, especially in persons at the highest risk for the disease (24, 25). We surmised that only a small number of obese study subjects along with the short period of follow-up in our study made it difficult to detect the protective effect of exercise.

BMI has been found to be a powerful predictor of NIDDM in studies of both men and women (26-30). Body fat distribution also has important effects on health. Recent studies have reported that abdominal obesity increases the risk of diabetes among men independently of BMI, confirming the previous data in cross-sectional studies (31-34). Measurements to assess fat distribution were not available in the study period with Asan cohort for this report.

An important limitation of this study is the small number of incident NIDDM cases in women. Only two incident NIDDM cases developed in women with BMI less than 23 kg/m², with a wide range of 95% confidence interval. For future investigations, a larger number of cases are needed to build appropriate groups according to BMI, and thus to reveal the effects of minimal obesity. The incidence of NIDDM in this study lacks an external validity because our study subjects do not necessarily represent the general Korean population. Even with these limitations, these data identified risk factors for the development of NIDDM in Korean population.

The average BMI of Korean population is relatively low. Overweight persons with BMI over 25 kg/m² comprise 16.7% of total population in men and 11.0% in women (35). Nonetheless, these data indicate that obesity is a risk factor for the development of NIDDM, and weight reduction would be effective for the primary prevention of NIDDM in Korea.

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