Supervised Exercise Program, BMI, and Risk of Type 2 Diabetes in Subjects With Normal or Impaired Fasting Glucose

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OBJECTIVE—To determine the association of regular exercise, BMI, and fasting glucose with the risk of type 2 diabetes and to predict the risk.

RESEARCH DESIGN AND METHODS—Korean subjects (n = 7,233; 40–79 years old) who were not diagnosed with diabetes at baseline were enrolled through the National Health Insurance Corporation. All participants underwent biennial examinations, and 1,947 of 7,233 subjects also underwent a 6-month program of moderate-intensity exercise (300 min/week) without dietary advice.

RESULTS—During follow-up (mean = 2 years), there were 303 incidents of type 2 diabetes in the nonexercise program group (n = 5,286) and 83 in the exercise program group (n = 1,947). After adjusting for confounders, the risk of type 2 diabetes was positively associated with BMI and inversely with regular exercise, especially among overweight/obese subjects. After further adjustment for BMI, the odds ratios for risk of diabetes associated without and with regular exercise were 1.00 and 0.77, respectively. Among subjects with normal fasting glucose, exercise reduced the diabetes risk; however, among those with impaired fasting glucose (IFG), the protective effect of exercise program group exhibited improved fasting glucose compared with the nonexercise program group and showed 1.5 kg of weight loss and a 3-cm decrease in waist circumference. Among overweight/obese subjects with unchanged fasting glucose, weight loss was greater in the exercise program group.

CONCLUSIONS—Regular exercise reduces the risk of type 2 diabetes in overweight/obese individuals. Particularly, regular exercise and weight or waist circumference control are critical factors for preventing diabetes in overweight/obese individuals with IFG.

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The benefits of exercise in preventing and treating type 2 diabetes are widely recognized (1). Exercise improves glycemic control, body composition, cardiorespiratory fitness, cardiovascular risk, physical functioning, and well-being in patients with type 2 diabetes or prediabetes (1–3). Regular exercise is therefore a key strategy in diabetes prevention. A number of large-scale, randomized, controlled trials have been performed to evaluate the effect of lifestyle modification in prediabetic populations (4–10), with the aim of reducing the incidence of type 2 diabetes and

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ameliorating risk factors associated with this disease. These lifestyle interventions, which generally included both physical activity and nutritional interventions, have been highly successful in preventing the onset of type 2 diabetes. Studies that failed to show improved glycemic control typically reported poor exercise compliance (11) or low-intensity exercise (12). However, most physical activity intervention studies focused on English speakers. Additional studies are needed to characterize ethnic and/or cultural differences in the risk of type 2 diabetes because most studies show lower physical activity levels in nonwhite compared with white populations (13). Accordingly, tailor-made interventions that take into account the different needs of various groups (e.g., language and culture) should be developed and evaluated. In this prospective cohort study, we evaluated the association of regular exercise, BMI, and glucose levels with the risk of type 2 diabetes in a Korean population. The exercise program was prescribed and delivered by qualified health professionals.

RESEARCH DESIGN AND METHODS

Study population

This 2-year, prospective cohort study included 7,233 Korean subjects (40-79 years old) who underwent biennial medical evaluations through the National Health Insurance Corporation (NHIC) (2007-2011). Major exclusion criteria included a diagnosis of diabetes or use of medications known to impair glucose tolerance. The procedure and results of screening, recruitment, and classification of the study subjects are shown in the flowchart (Supplementary Fig. 1). A total of 21,673 subjects underwent both basal and biennial medical evaluations between 2007 and 2011. Type 2 diabetes was not detected in 7,576 subjects (35.0%), and they were subdivided into the exercise (n = 2,290) and nonexercise (n = 5,286) program groups. Among the exercise program group, 1,947 subjects met the requirements of the

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exercise program. At any period during the 2-year study, 1,947 of the subjects participated in a 6-month exercise program provided by the Health Promotion Center of the NHIC that consisted of 300 min/week of moderate-intensity exercise without specific dietary advice. The remaining 5,286 subjects underwent the biennial examinations only. At the end of the 2-year study, participants were subdivided into groups according to fasting glucose levels: normal fasting glucose (NFG), impaired fasting glucose (IFG), and type 2 or new-onset diabetes based on the biennial medical evaluation results. New-onset diabetes was defined as diagnosed (i.e., use of antidiabetic medication) or undiagnosed (American Diabetes Association criteria of fasting glu $cose \ge 126 \text{ mg/dL} [7.0 \text{ mmol/L}]$). IFG was defined as a fasting glucose level of 100-126 mg/dL (5.55-6.99 mmol/L) and NFG as a fasting glucose level <100 mg/dL (5.55 mmol/L). Written informed consent was obtained from all participants before screening, consistent with the Helsinki Declaration.

Exercise program

The exercise program was prescribed and delivered by qualified health professionals. All subjects who volunteered to participate in the exercise program were screened for eligibility through questionnaires and the basic medical examination before enrollment. Based on the screening result, eligible participants underwent a physical fitness test that included a handgrip strength measurement and sit-up test for muscular strength, a standing on one leg with eyes closed test for balance, and the use of a cycle ergometer for testing cardiorespiratory endurance. After the baseline anthropometric and fitness measurement, the exercise physiologist prescribed a personalized program (i.e., exercise type, intensity, and frequency) to each person. Intensity of aerobic exercise ranged between an initial exercise intensity of 65% heart rate maximum to, and upward of, 85% heart rate maximum. Intensity of resistance exercise was 50% of one repetitive maximum value and trained in one set (12-15 repetitions). Exercise frequency was three times per week for 6 months. The programs were performed for 6 months and consisted of warm-up (10–15 min), aerobic (25–30 min; e.g., treadmill or cycling), resistance (10-15 min; e.g., bench press, arm curl, bent-knee sit-up, etc.), and cool-down (10-15 min; general relaxation and stretching) exercises.

Data collection: anthropometric and biochemical parameters

The NHIC biennial examinations performed by the medical staff at local hospitals follow a standard procedure. Participants were asked 1) to describe health habits, including cigarette smoking and alcohol consumption and 2) whether they were treated for diabetes, and the date of diagnosis if they answered yes. Anthropometric and biochemical measurements included BMI, waist circumference, and blood pressure. Serum glucose and lipid profiles (triglycerides and total, LDL, and HDL cholesterol) were measured after fasting.

Statistical analyses

Each participant's fasting glucose status was classified as NFG, IFG, or type 2 diabetes based on results of the biennial examinations. At the end of the study, any changes from baseline were categorized as improvement (IFG to NFG), no change (NFG to NFG and IFG to IFG), or deterioration (NFG to IFG and NFG/IFG to diabetes); the last two categories (i.e., NFG/ IFG to diabetes) were combined because of small numbers in the NFG-to-diabetes category (14).

Statistical analyses were performed using SPSS version 12.0 for Windows (SPSS Inc., Chicago, IL). Frequency was analyzed by χ^2 test. Differences in clinical variables between groups (exercise vs. nonexercise program group) were evaluated by independent Student t test, and a general linear model test was used to adjust for baseline values or smoking/drinking status and antihypertensive drug use. A paired Student *t* test was used to evaluate the effects of the exercise program. After adjusting for confounding factors, the association of type 2 diabetes with exercise, BMI, and fasting glucose concentrations was evaluated using a logistic regression model to estimate odds ratios (ORs) (95% CIs). Logistic regression analysis was used to determine the relationship between IFG and type 2 diabetes status and participation in an exercise program. Continuous variables were expressed as mean \pm SE, and categorical variables were expressed as absolute numbers and percentages. A two-tailed value of P < 0.05 was considered significant.

RESULTS

Clinical characteristics at baseline and 2-year follow-up

We measured compliance to the exercise program and only included subjects that attended at least 60 of the intervention periods (72 times/6 months). All subjects who were affiliated with the exercise program group underwent a 6-month program of moderate-intensity exercise (300 min/ week) without dietary advice. Almost all of the basal physical fitness test characteristics in the exercise program group (hand-grip strength measurement, sit-up test, standing on one leg with eyes closed test, and trunk flexion forward test) were improved at the end of the 2-year study (Supplementary Table 1). Clinical characteristics of participants at baseline and at the 2-year follow-up are shown in Table 1. No significant differences were found between the two groups (exercise vs. nonexercise program group) in sex distribution, age, BMI, blood pressure, and serum glucose at baseline. However, the exercise program group had lower proportions of current smokers, current drinkers, and antihypertensive drug users compared with the nonexercise program group. Mean total cholesterol level at baseline was slightly but significantly higher in the exercise program group after adjusting for smoking, drinking, and antihypertensive drug use.

At the end of the 2-year study, the nonexercise program group showed significantly increased fasting glucose and total cholesterol levels, but decreased blood pressure. The exercise program group also showed significantly increased fasting glucose levels, but decreased BMI, waist circumference, and blood pressure. After adjusting for baseline values, changes in BMI, waist circumference, and blood pressure were significantly lower in the exercise program group compared with the nonexercise program group. At the 2-year follow-up, BMI and blood pressure were lower in the exercise program group than the nonexercise program group after adjusting for smoking, drinking, and antihypertensive drug use (Table 1).

Association between type 2 diabetes and exercise, BMI, and fasting glucose

During a mean follow-up period of 2 years, there were 303 incident cases of type 2 diabetes in the nonexercise program group and 83 in the exercise program group (Table 2). The risk of type 2 diabetes after adjusting for confounding factors (age, sex, smoking/drinking status, systolic and diastolic blood pressure, total cholesterol, and antihypertensive drug use) significantly decreased with regular exercise. After further adjustment for BMI, the ORs for risk of diabetes associated without and with regular exercise were 1.00 and 0.77, respectively

Table 1—Participant characteristics at baseline and at the end of the 2-year study

	Nonexercise program group $(n = 5,286)$	P^{a}	Exercise program group $(n = 1,947)$	P ^a	P^{b}	P ^c
Male/female (n, %)	796/4,490 (15.1/84.9)	-	294/1,653 (15.1/84.9)	-	0.970	-
Age (years)	56.0 ± 0.09		56.0 ± 0.14		0.872	
Current smokers, n (%)	257 (4.9)		45 (2.3)		< 0.001	
Current drinkers, n (%)	1,037 (19.6)		315 (16.2)		0.001	
Antihypertensive drug, <i>n</i> (%)	2,132 (40.3)		701 (36.0)		0.001	
BMI (kg/m^2)	, - ()					
Baseline	25.0 ± 0.04		25.0 ± 0.06		0.406	
Follow-up	25.0 ± 0.04		24.7 ± 0.06		0.013	
Change	-0.02 ± 0.02	0.271	-0.26 ± 0.03	< 0.001	< 0.001	< 0.001
Waist circumference (cm)						
Baseline	81.0 ± 0.17		81.1 ± 0.26		0.113	
Follow-up	80.9 ± 0.17		80.2 ± 0.26		0.373	
Change	-0.11 ± 0.12	0.374	-0.87 ± 0.18	< 0.001	0.001	< 0.001
Blood pressure (mmHg)						
Systolic blood pressure						
Baseline	125.3 ± 0.23		124.8 ± 0.34		0.940	
Follow-up	124.9 ± 0.22		123.0 ± 0.30		< 0.001	
Change	-0.46 ± 0.23	0.049	-1.83 ± 0.34	< 0.001	0.001	< 0.001
Diastolic blood pressure						
Baseline	77.7 ± 0.15		77.3 ± 0.23		0.622	
Follow-up	77.2 ± 0.14		76.2 ± 0.21		0.003	
Change	-0.46 ± 0.15	0.003	-1.04 ± 0.24	< 0.001	0.027	0.001
Glucose (mg/dL)						
Baseline	93.0 ± 0.16		92.7 ± 0.24		0.610	
Follow-up	96.1 ± 0.20		95.3 ± 0.32		0.150	
Change	3.09 ± 0.20	< 0.001	2.58 ± 0.31	< 0.001	0.297	0.063
Total cholesterol (mg/dL)						
Baseline	204.4 ± 0.51		206.7 ± 0.88		0.034	
Follow-up	205.8 ± 0.52		205.5 ± 0.87		0.527	
Change	1.48 ± 0.52	0.005	-1.24 ± 0.83	0.135	0.005	0.074

Data are mean ± SE unless otherwise indicated. ^aP values derived from paired Student *t* test. ^bP values derived from general linear model after adjusting for smoking, drinking, and antihypertensive drug. ^cP values derived from general linear model after adjusting for baseline values.

(P = 0.038 for trend). Overweight/obesity was associated with a 1.80-fold increased risk for type 2 diabetes compared with normal weight after adjusting for confounding factors and exercise (P < 0.001 for trend). Subjects with IFG showed a 5.98-fold higher risk of developing type 2 diabetes than subjects with NFG after adjustment for all covariates (P < 0.001 for trend).

In subgroup analyses based on BMI (<25 and \geq 25 kg/m²) (Supplementary Fig. 2*A*), the inverse association between exercise and risk of type 2 diabetes was stronger for overweight/obese subjects. The inverse association between exercise and risk for type 2 diabetes persisted in subgroup analyses based on glucose levels (NFG and IFG) (Supplementary Fig. 2*B*). The positive association between BMI and risk of type 2 diabetes was confirmed in subjects with NFG and IFG (Supplementary Fig. 2*C*).

The joint association of exercise, BMI, and glucose levels with the risk of type 2

diabetes after adjusting for confounding factors is shown in Supplementary Fig. 3. Among subjects with NFG, BMI was positively associated with the protective effect of exercise. However, among those with IFG, the protective effect of exercise was only found in overweight/obese subjects. Compared with normal-weight subjects with NFG in the exercise program group, overweight/obese subjects with IFG in the nonexercise program group showed a 16.3-fold higher risk of developing type 2 diabetes. The relative effect of obesity and exercise on diabetes risk was larger among subjects with NFG, but the absolute effect was larger among subjects with IFG.

Mean changes in body weight and waist circumference according to fasting glucose level change, exercise, and BMI

Among overweight/obese subjects, significantly fewer subjects showed improved fasting glucose (from IFG to NFG) during the 2-year study in the exercise program group, although body weight fell by about 1.5 kg and waist circumference by 3 cm (Fig. 1). Among overweight/obese subjects whose fasting glucose status did not change, weight loss was greater in the exercise program group. Among normal-weight subjects with unchanged NFG status, reductions in body weight and waist circumference were significantly greater in the exercise program group.

Regular exercise as an independent predictor of IFG and type 2 diabetes

Based on these results, we performed logistic regression analysis to determine independent predictors of IFG and type 2 diabetes (Table 3). Age, baseline BMI, \triangle weight, baseline waist circumference, \triangle waist circumference, exercise, baseline glucose level, baseline blood pressure (diastolic and systolic), \triangle blood pressure (diastolic and systolic), baseline total cholesterol, and

Table 2-Association between type 2 diabetes and exercise, BMI, and fasting glucose concentration

	New cases of type 2		OR (95% CI)			
	diabetes, n (%)	Subjects (n)	Model 1*	Model 2†	Model 3	
Exercise program						
No exercise program	303 (5.7)	5,286	1.00	1.00	1.00‡	
Exercise program	83 (4.3)	1,947	0.73 (0.57-0.94)	0.76 (0.59-0.98)	0.77 (0.60-1.00)	
P value			0.014	0.036	0.038	
BMI (kg/m ²)						
<25	132 (3.6)	3,631	1.00	1.00	1.00‡‡	
≥25	254 (7.1)	3,602	2.01 (1.62-2.50)	1.80 (1.44-2.24)	1.80 (1.45-2.24)	
P value			< 0.001	< 0.001	< 0.001	
Fasting glucose level						
Normal (<100 mg/dL)	124 (2.3)	5,356	1.00	1.00	1.00§	
Impaired (≥100 mg/dL)	262 (14.0)	1,877	6.85 (5.49-8.54)	6.30 (5.04-7.89)	5.98 (4.77-7.48)	
P value			< 0.001	< 0.001	< 0.001	

*Unadjusted. †Adjusted for age, sex, smoking and drinking status, systolic and diastolic blood pressure, total cholesterol, and antihypertensive drug use. ‡Adjusted also for BMI. ‡‡Adjusted also for BMI and exercise program.

 \triangle total cholesterol were evaluated. Regular exercise was found to be an independent predictor of IFG and type 2 diabetes ($\beta = -0.037 \pm 0.020$; P = 0.023) together with known risk factors for IFG and metabolic syndrome (baseline waist circumference, P < 0.001; \triangle waist circumference, P = 0.001; baseline glucose

level, P < 0.001; baseline systolic blood pressure, P = 0.002; baseline total cholesterol, P = 0.019; and \triangle total cholesterol, P < 0.001).

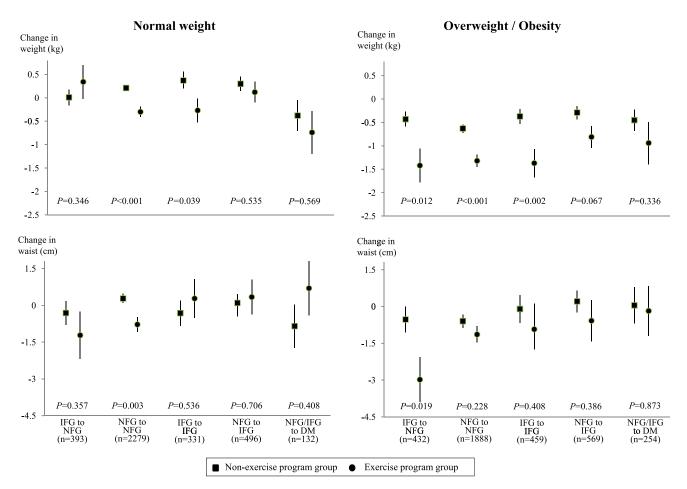


Figure 1—Mean changes in body weight and waist circumference according to participation in the 6-month exercise program, BMI (normal weight vs. overweight/obese), and changes in fasting glucose. Data are expressed as mean \pm SE. DM, type 2 diabetes. (A high-quality color representation of this figure is available in the online issue.)

Table 3—Results of logistic regression analysis for IFG and diabetes status as dependent variables

Variable	Regression coefficient	SE	Р
All participants ($n = 7,233$)			
Exercise (yes/no)	-0.037	0.020	0.023
Fasting serum glucose	0.369	0.001	< 0.001
Δ Weight	0.016	0.003	0.369
BMI	-0.017	0.005	0.539
Δ Total cholesterol	0.070	0.000	< 0.001
Δ Systolic BP	0.038	0.001	0.163
Δ Diastolic BP	0.001	0.001	0.975
Age	0.025	0.002	0.140
Systolic BP	0.098	0.001	0.002
Diastolic BP	-0.018	0.002	0.581
Waist circumference	0.134	0.002	< 0.001
Δ Waist circumference	0.069	0.002	0.001
Total cholesterol	0.044	0.000	0.019

 Δ , Changes are differences between baseline and 2 years. Adjusted $R^2 = 0.191$; P < 0.001. BP, blood pressure.

CONCLUSIONS—In this 2-year study, a 6-month exercise program consisting of 300 min/week of moderate-intensity exercise without dietary changes resulted in a 23% reduction in the incidence of type 2 diabetes. This inverse association between exercise and risk of type 2 diabetes was stronger among overweight/obese subjects than normal-weight subjects. In addition, the exercise program group showed improved fasting glucose levels (from IFG to NFG: normal-weight subjects in the exercise program group, 46.0%; overweight/obese subjects in the exercise program group, 54.0%). Improved fasting glucose was associated with reductions in waist circumference and BMI: this reduction was significantly greater in the exercise program group, suggesting that regular exercise indirectly reduces the risk of type 2 diabetes through decreased body weight or improved body fat distribution in overweight/obese subjects. Exercise has been shown to facilitate weight loss (15) but more strongly influences abdominal adiposity (16). The overweight/ obese subjects in the exercise program group whose fasting glucose values improved or remained the same showed a greater reduction in body weight. This result is consistent with previous reports showing that being overweight or physically inactive increases the risk of type 2 diabetes (6), demonstrating the need for appropriate exercise interventions for this group.

A number of studies have demonstrated the benefits of exercise on glucose regulation. The U.S. Diabetes Prevention Program reported a 58% reduction in the incidence of type 2 diabetes with an average of 2.8 years (range, 1.8-4.6) of lifestyle intervention that prescribed 150 min/week of moderate-intensity exercise and a dietary program designed to induce a 7% weight loss (6). A similar risk reduction of 58% was associated with lifestyle changes in the Finnish Diabetes Prevention Study (5); and in Asian Indians with impaired glucose tolerance, lifestyle modifications, including 210 min/week of brisk walking and dietary modifications (i.e., reduction in total calorie intake and total fat intake, avoidance of simple sugars and refined carbohydrates, and inclusion of fiber-rich food), resulted in a 28.5% reduced risk of incident diabetes (7). Hu et al. (17) also reported an inverse association between physical activity and the risk of type 2 diabetes for nonobese subjects with normal glucose regulation, as well as subjects who were either obese or showed impaired glucose regulation (mean follow-up = 9.4years). However, several studies reported that glycemic control did not improve with lifestyle modification and drug therapy (11,12). Krousel-Wood et al. (11) reported that exercise interventions have the potential to reduce BMI in patients with diabetes but not reduce HbA1c. Khan et al. (12) reported that exercise in conjunction with oral drug therapy prescribed for the individual with type 2 diabetes did not directly modify HbA_{lc} levels. These discrepant results might be partly due to differences in the duration of follow-up, prescribed nutritional therapy, and prescribed exercise volume and/or intensity. In the current study, an exercise program (without nutrition intervention) was prescribed and

monitored by a qualified health care professional. A strong inverse association between exercise and risk of type 2 diabetes was found among overweight/obese subjects.

Several previous studies reported that impaired glucose regulation appears to best predict future diabetes (18-21). Lifestyle changes have been shown to be effective in preventing both diabetes and obesity in high-risk adults with impaired glucose tolerance (4-6). Compared with normal-weight subjects with NFG who participated in the regular exercise program in the current study, the risk of developing type 2 diabetes for overweight/ obese subjects with IFG was 16.3-fold higher in the nonexercise program group and 10.8-fold higher in the exercise program group. This finding that regular exercise reduces the risk of diabetes among obese individuals with IFG is consistent with results of previous clinical trials (4-6).

The strength of the current study was that the exercise program was prescribed and monitored by a qualified health care professional, whereas previous studies often used self-reports of physical activity, which are less accurate and usually result in bias. The limitation of the current study was the lack of randomization of participants to groups (exercise vs. nonexercise program group). In addition, we did not perform the 2-h oral glucose tolerance test on the biennial medical evaluations and during the supervised exercise program study; therefore, the criteria for diabetes (i.e., patient history or fasting glucose levels) may have included some cases of asymptomatic diabetes at baseline or misclassified the glucose status. Misclassification of diabetes would weaken the association between exercise and BMI and the risk of type 2 diabetes. Despite these limitations, the current study shows that regular exercise can reduce the risk of type 2 diabetes in individuals who are overweight or obese, even without dietary changes. The findings indicate that regular exercise and reductions in weight or waist circumference are critical factors in diabetes prevention among overweight or obese individuals with IFG

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