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Original Article

Effects of Changes in Obesity and Exercise on the Development of Diabetes and Return to Normal Fasting Plasma Glucose Levels at One-Year Follow-up in Middle-Aged Subjects with Impaired Fasting Glucose

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Abstract

Objectives: Borderline diabetes, a precursory condition of diabetes, is an important issue in the prevention of diabetes. The aim of the present study was to clarify the effects of one-year changes in obesity and exercise on the development of diabetes or return to normal fasting plasma glucose (FPG) levels among middle-aged people with impaired fasting glucose (IFG) at baseline.

Methods: Among those who attended a basic health examination in 1997, we selected 1,620 subjects who showed impaired fasting glucose (FPG of 110 mg/dl or higher) and had complete data on height, weight and exercise. At the one-year follow-up (in 1998), 1,099 of those subjects attended a health examination; FPG, height, weight and exercise were evaluated for 731 subjects. Subjects were classified into the following three groups, on the basis of changes in FPG during the year between the two examinations: developing diabetes (DM), remaining IFG, and returning to normal (WNL).

Results: Among those who were initially obese, there was a significant difference in the proportions of DM, IFG and WNL between those with and without improvement in obesity in the year preceding the follow-up ($p<0.05$). Those with improvement in obesity showed a significantly higher tendency to return to WNL than those without improvement in obesity. Multiple logistic regression analysis showed that those with improvement in obesity had a significantly higher odds ratio (2.17) to return to WNL ($p=0.015$). Among those who were initially not obese, there was no significant association between changes in obesity and developing DM or returning to WNL. No significant association was observed between changes in exercise and developing DM or returning to WNL.

Conclusion: The present findings suggest that, among obese IFG subjects, improvement in obesity is associated with returning to normal plasma glucose. Weight control may be important for the normalization of borderline diabetes.

Key words: impaired fasting glucose (IFG), diabetes mellitus, obesity, exercise, follow-up study

Introduction

Borderline diabetes [also known as impaired glucose tolerance (IGT)], which is a precursory condition of type 2 diabetes mellitus (DM), is considered a warning of the onset of type 2 DM[1,2]. It has been reported that the five-year transition rate from borderline diabetes to overt type 2 DM is 34.1%[3], which is 10–20 fold higher than the rate of transition of normal glucose-tolerant individuals to type 2 DM[4]. The normalization of borderline diabetes thus qualifies as a goal in the prevention of type 2 DM.

Many studies have suggested that obesity and physical inactivity are associated with the transition from borderline diabetes to overt type 2 DM[5–8]. Obesity and type 2 DM are closely related[9,10]. It has been reported that, in an obese state, the number of insulin receptors present in the cell membranes of target organs decreases[11]. However, this is not an irreversible abnormality, and the number of receptors normalizes if obesity is improved[12,13]. It has also been reported that pancreatic β cells recover when insulin sensitivity is improved and insulin demand volume is reduced due to improvements in obesity[14].

Exercise lowers blood glucose during and after exercise

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(acute effects), and increases insulin sensitivity due to continuation of the short-term effects (chronic effects)[15]. The result of these effects is that a small amount of insulin secretion can be utilized effectively[15]. Exercise for long durations burns fat, which may result in improvements in obesity. Continued exercise increases the amount of facilitative glucose transporters (GLUT4) in muscle cells, thereby improving glucose tolerance[15]. Thus, it is thought that improvements in obesity or exercise are effective for treating type 2 DM. It is generally accepted that improvement in obesity and exercise are also effective for normalization of borderline diabetes (glucose intolerance), which is a precursor of overt type 2 DM.

While several other modifiable life-style-related risk factors for the development of type 2 DM have been identified, including nutrition and drinking[16,17], the Japan Public Health Council has reported that improvements in obesity and physical exercise are strongly indicated as factors for the prevention of the onset and progression of type 2 DM. However, there has been little research on the effects of changes in obesity and exercise on the transition from borderline diabetes (IGT) to overt type 2 DM. Most studies that have associated obesity or exercise with the subsequent development of type 2 DM have not taken into consideration the effects of changes in obesity or exercise[3,4,18–20]. No study has examined the effects of obesity or exercise on normalization of borderline diabetes (IGT); i.e. transition from borderline to normal glucose tolerance.

The latest diagnostic criteria for type 2 DM define impaired fasting glucose (IFG) as a subtype of borderline diabetes[21,22]. We conducted a one-year prospective study to examine the effects of changes in obesity and exercise on the development of type 2 DM and the return to normal among middle-aged people with IFG at baseline. While it may take a long time to observe changes in IFG associated with improvement in obesity or exercise, the aim of the present study was to examine whether improvement in obesity or exercise during a short period (one-year) predicts transition to type 2 DM or a return to normal glucose tolerance.

Subjects and Methods

Subjects

In 1997, O-city in Okayama Prefecture conducted basic health examinations in accordance with the Elderly Health Law. A total of 44,478 people aged 40 years or older participated in the health examinations. People who could not be measured for fasting plasma glucose, and were thus measured only for postprandial blood glucose, were excluded because it was not clear how many hours had elapsed postprandially when the blood sample was taken. Fasting plasma glucose (FPG), height and weight were measured for 25,268 of the participants. They were asked to complete a questionnaire concerning exercise, and we excluded the 361 people who did not respond to these exercise questions. We further excluded 1,408 people with a current or past medical history of diabetes or a family history of diabetes. Among the remaining 23,153 people, 1,620 showed FPG of 110 mg/dl or greater and were diagnosed as IFG according to the diagnostic criteria[21,22]. These 1,620 people were the subjects of the present study. At the one-year follow-up, 1,099 (67.8%) of these baseline subjects attended a health examination at which their blood glucose, height and weight were measured; FPG was obtained from 815 subjects. They were also asked to complete a questionnaire about exercise (identical to the one used at the baseline examination). We excluded the 84 subjects who did not complete the questionnaire. The remaining 731 subjects were classified into three groups: within normal limits (WNL), diagnosed as IFG, and diagnosed as DM, according to the diagnostic criteria used at the baseline examination[21,22].

We did not obtain informed consent from the participants. However, the findings were handled in a strictly confidential manner, under the close supervision and direction of the public health center where the health examinations took place. Furthermore, information which could be used to identify individual subjects (e.g. name or identification number) was deleted from the data used in the analysis.

Diagnosis of IFG and diabetes

The Expert Committee of the American Diabetes Association (ADA) and the working group of the World Health Organization (WHO) proposed new criteria for the diagnosis of DM in 1997 and 1998, respectively[21,22]. The ADA classified glycemia into the following categories: DM, impaired glucose tolerance (IGT), impaired fasting glucose (IFG) and normoglycemia.

Measurement of obesity and exercise

Obesity measurement was based on the 1986 evaluation table of obesity and emaciation, and subjects were classified into one of five categories: 'definitely obese', 'tending to obesity', 'normal', 'slim', and 'thin'. Among those who were initially obese (i.e. 'definitely obese' or 'tending to obesity' category at baseline), improvement of obesity was defined as moving from the 'definitely obese' category (at baseline) to any of the other four categories (at the follow-up), or moving from the 'tending to obesity' category (at baseline) to the 'normal', 'slim' or 'thin' category (at the follow-up). All other initially obese subjects were defined as 'staying obese'. Among those who were initially non-obese (i.e. 'normal', 'slim', or 'thin' category at baseline), those who moved to either of the two 'obese' categories at the follow-up were defined as 'getting obese'. All other initially non-obese subjects were defined as 'not getting obese'.

Leisure-time physical exercise was evaluated in accordance with the survey of diabetes by the Ministry of Health and Welfare[23]. Subjects were first asked whether they had been exercising regularly, for 30 minutes at a time, for one year or longer. Those who gave a positive answer to this question were then asked to report their exercise frequency: (1) everyday, (2) two times or more per week, or (3) one time per week or less. Habitual exercise was defined as exercise at least two times per week, for at least 30 minutes each time, during the entire preceding one year or longer[23]. Based on the combination of responses to questions at the baseline and the follow-up, exercise was defined as follows: 'continuing', when the response was 'yes' at the baseline and 'yes' at the follow-up; 'stopped', when the response was 'yes' at the baseline and 'no' at the follow-up; 'started', when the response was 'no' at the baseline and 'yes' at the follow-up; 'no exercising', when the response was 'no' at the baseline and 'no' at the follow-up.

We also included gender and age (as a continuous variable) as variables in the analysis.

Statistical analysis

Among subjects who were initially obese, we compared the

Table 1 Changes in obesity, and the proportions of subjects developing diabetes (DM) or returning to normal (WNL), at one-year follow-up among middle-aged people with impaired fasting glucose at baseline

Obesity change	Number of subjects	At one-year follow-up*			Chi-square test (df=2)
		WNL	IFG	DM	
Definitely obese or tending to obesity at baseline (n=265):					
Staying obese	194	85 (43.8%)	86 (44.3%)	23 (11.9%)	p=0.03
Improvement of obesity	71	42 (59.2%)	19 (26.8%)	10 (14.1%)	
Normal, slim or thin at baseline (n=466):					
Not getting obese	434	233 (53.7%)	158 (36.4%)	43 (9.9%)	p=0.73
Getting obese	32	19 (59.4%)	11 (34.4%)	2 (6.3%)	

* WNL, within normal limit [fasting plasma glucose (FPG) <110]; IFG, impaired fasting glucose (110≤FPG<126); DM, diabetes (126≤FPG).

Table 2 Changes in exercise, and the proportions of subjects developing DM or returning to WNL, at one-year follow-up among middle-aged people with impaired fasting glucose at baseline

Exercise change	Number of subjects	At one-year follow-up*			Chi-square test (df=2)
		WNL	IFG	DM	
Physically active at baseline (n=258):					
Continuing	181	96 (53.0%)	70 (38.7%)	15 (8.3%)	p=0.38
Stopped	77	34 (44.2%)	34 (44.2%)	9 (11.7%)	
Physically inactive at baseline (n=514):					
Started	99	56 (56.6%)	32 (32.3%)	11 (11.1%)	p=0.66
No exercising	374	193 (51.6%)	138 (36.9%)	43 (11.5%)	

* WNL, within normal limit; IFG, impaired fasting glucose; DM, diabetes.

proportional representation of the three groups classified on the basis of changes in FPG (developing DM, remaining IFG and returning to WNL), between subjects with improvement in obesity and those without improvement in obesity (chi-square test, d.f.=2). Among subjects who were not initially obese, we compared the proportional representation of these three groups between subjects not getting obese and those getting obese (chi-square test, d.f.=2). A similar comparison was made for exercise; i.e. between those subjects who continued exercise and those who stopped exercise, and between those who started exercise and those who stayed physically inactive (chi-square test, d.f.=2).

For subjects who were initially obese and those who were initially not obese, we conducted separate multiple logistic regression analyses of developing DM vs. remaining IFG, including variables for gender, age and change in obesity; we also performed separate multiple logistic regression analyses of returning to WNL vs. remaining IFG. Among subjects who exercised at baseline and those who did not exercise at baseline, we conducted separate multiple logistic regression analyses of developing DM vs. remaining IFG (and of returning to WNL vs. remaining IFG), including variables for gender, age and changes in exercise.

The chi-square test was used to test for associations between the four categories of changes in obesity (i.e. staying obese, improvement in obesity, not getting obese and getting obese) and the four categories of changes in exercise (i.e. continuing, stopped, started and no exercising). The P-value for statistical significance was set at 0.05.

Results

Of the final 731 subjects, there were 270 males and 461 females who had IFG at baseline; their average age was 66.8 years, and their ages ranged from 40 to 94. At the one-year follow-up, a total of 78 (10.7%) developed DM, while 274 (37.5%) remained IFG and 379 (51.8%) returned to WNL.

Table 1 shows that there was a significant difference in the proportion of the three groups classified on the basis of changes in FPG (developing DM, remaining IFG and returning to WNL) between those with improvement in obesity and those without improvement in obesity. Those with improvement in obesity had a significantly greater tendency to return to WNL than those without improvement in obesity (p=0.010: data not shown).

Table 2 shows that there was no significant difference in the proportion of the three groups classified on the basis of changes in FPG (developing DM, remaining IFG and returning to WNL) between those who continued exercise and those who stopped exercise, or between those who started exercise and those who stayed physically inactive.

Multiple logistic regression analysis showed that those with improvement in obesity had a significantly higher odds ratio (2.17) to return to WNL than those staying obese (p=0.015: data not shown) (Table 3). No other significant differences in odds ratios for developing DM or returning to WNL were observed for changes in obesity or exercise (Tables 3 and 4).

There was no significant association between the four categories of changes in obesity and the four categories of changes in exercise.

Discussion

The findings of the present study showed that obese subjects who initially had IFG were more likely to return to normal fasting glucose when their obesity was improved than when they stayed obese. This tendency was still significant after controlling for

Table 3 Association of changes in obesity with development of DM or return to WNL at one-year follow-up, among middle-aged people with impaired fasting glucose at baseline; multiple logistic regression analysis controlling for gender and age (odds ratios and 95% confidence intervals in parentheses)[$]

Obesity change	Development of DM vs. Remaining IFG	Return to WNL vs. Remaining IFG
Definitely obese or tending to obesity at baseline:		
Change in obesity:		
Staying obese	1.00	1.00
Improvement of obesity	0.52 (0.21–1.26)	2.17 (1.16–4.05)*
Gender (male)	1.04 (0.45–2.36)	0.84 (0.49–1.44)
Age (10-year age difference)	1.01 (0.97–1.05)	0.98 (0.96–1.01)
Normal, slim or thin at baseline:		
Change in obesity:		
Not getting obese	1.00	1.00
Getting obese	1.53 (0.32–7.26)	1.16 (0.53–2.50)
Gender (male)	1.21 (0.61–2.39)	1.02 (0.68–1.54)
Age (10-year age difference)	0.98 (0.94–1.01)	0.99 (0.97–1.01)

$ WNL, within normal limit; IFG, impaired fasting glucose; DM, diabetes.
* $p<0.05$.

Table 4 Association of changes in exercise with development of DM or return to WNL, at one-year follow-up among middle-aged people with impaired fasting glucose at baseline; multiple logistic regression analysis controlling for gender and age (odds ratios and 95% confidence intervals in parentheses)*

Exercise change	Development of DM vs. Remaining IFG	Return to WNL vs. Remaining IFG
Physically active at baseline:		
Change in exercise:		
Continuing	1.00	1.00
Stopped	0.81 (0.32–2.06)	0.70 (0.39–1.24)
Gender (male)	0.95 (0.38–2.34)	0.98 (0.59–1.70)
Age (10-year age difference)	1.00 (0.95–1.05)	0.98 (0.99–1.05)
Physically inactive at baseline:		
Change in exercise:		
Started	1.00	1.00
No exercising	1.18 (0.53–2.62)	0.82 (0.50–1.34)
Gender (male)	1.29 (0.41–1.48)	0.91 (0.60–1.39)
Age (10-year age difference)	0.99 (0.98–1.04)	0.99 (0.97–1.01)

* WNL, within normal limit; IFG, impaired fasting glucose; DM, diabetes.

gender and age. This finding is consistent with those of previous cross-sectional studies, in which it was observed that obesity was associated with glucose intolerance. In this study, subjects with type 2 DM or a personal or family history of type 2 DM were excluded from analysis. We studied the transition from IFG, which is a precursor state of type 2 DM, and these underlying abnormalities may be more reversible in IFG than in overt type 2 DM. The present findings suggest that improvement in obesity is associated with returning to normal fasting glucose among those who initially had IFG.

We failed to clarify whether improvement of obesity suppresses development of type 2 DM. Previous studies reported that obesity at baseline is a predictor for subsequent development of type 2 DM[3,4,18,19]. This tendency was also observed in our study [12.5% rate of transition for those who were initially obese (n=265) and 9.6% for those who were not initially obese (n=466)], although it was not significant. Improvement in obesity lasting only one year, after long-term obesity (as measured at the baseline), may not effectively prevent development of type 2 DM. However, only a small number of subjects developed type 2 DM in our study, and this may be the reason for the observed non-significant association.

Among those who were not initially obese, changes in obesity were not associated with the transition from IFG. The transition from IFG may be less sensitive to changes in obesity in those who are not initially obese than in those who are initially obese, suggesting that the underlying mechanisms of IFG are different for obese and non-obese subjects.

In the present study, changes in exercise were not significantly associated with developing type 2 DM or returning to normal fasting glucose. Effects of exercise on the transition from IFG may be weaker than the effects of obesity. Previous studies reported that exercise habits at baseline predict the development of type 2 DM[24]. Although not significant, we found that those who continued exercising had both a higher tendency to return to WNL and a reduced tendency to develop DM than those who stopped exercising. These same tendencies were seen for those who started exercising, compared with those who stayed physically inactive. With a greater number of subjects, these tendencies may reach significance. In addition, we measured exercise only dichotomously; i.e. whether or not a subject exercised at least two times a week for at least 30 minutes each time. It is known that, when exercise is prescribed for treating type 2 DM, in addition to the frequency and duration, exercise intensity (based on pulse rate or exercise exchange table) is an important factor in improving insulin sensitivity. We only measured leisure-time exercise, excluding physical activity at work. The method we used for measuring exercise has not been thoroughly tested for reliability and validity. These limitations in our measurements, and the limited time period between baseline and follow-up, may be the reason for some of our non-significant findings.

The present study has limitations in addition to those already stated above. First, we only measured IFG, and did not make a full diagnosis of IGT. Some subjects with IFG may not have IGT. Second, we did not assess eating or drinking habits, which may be primary factors underlying obesity change. In the present study, subjects were not questioned about diet; i.e. the relationship between eating habits and blood glucose normalization was not assessed. Third, people who could not be measured for fasting plasma glucose, or were measured only for postprandial blood glucose, were excluded from the study. The significance of this last point is that, if a special group of subjects (those who had not fasted overnight) had tended to be excluded from the study, this might have resulted in a selection bias. Finally, although we selected subjects who were diagnosed with IFG, they may not have strictly fasted before the examinations. This might have resulted in a misclassification bias. There was the possibility of random errors in the diagnosis of IFG, due to meals eaten on the day before the examination[25]. A future study is needed to verify the present findings. Such a study should include a large number of subjects, and more precise diagnosis of IFG and other variables, such as exercise and diet.

In conclusion, the present study demonstrated that improvement in obesity is an important factor in returning to normal FPG levels, among subjects with IFG who are obese at baseline. It is generally understood that energy intake (diet) and energy expenditure (exercise) are factors involved in the changes in obesity. The

present study failed to show that exercise is associated with returning to normal FPG levels. However, as described above, there were limitations to our methods for measuring exercise. It is still not clear whether diet is a more important factor than exercise in improvement in obesity. Also, we did not examine changes in diet among the subjects. Thus, it was not clarified whether changes in diet were responsible for the changes in obesity and improvement of FPG that were observed. In future studies, it would be instructive to examine which of the following is most effective in improving FPG levels through improvement in obesity: control of diet, exercise, or a combination of the two.

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