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Effect of Short-Term Low-Intensity Exercise on Insulin Sensitivity, Insulin Secretion, and Glucose and Lipid Metabolism in Non-Obese Japanese Type 2 Diabetic Patients

Abstract

The aim of the present study was to investigate the effects of short-term physical exercise that did not change body mass on insulin sensitivity, insulin secretion, and glucose and lipid metabolism in 39 non-obese Japanese type 2 diabetic patients. Insulin sensitivity and insulin secretion were estimated with homeostasis model assessment insulin resistance (HOMA-IR) and HOMA-B-cell function proposed by Matthews et al., respectively. All patients were hospitalized and were engaged in low-intensity exercise that consisted of walking and dumbbell exercise for successive 7 days. There were no changes in hospital diet and the dose of any medications used throughout the study. Fasting glucose, insulin, and lipids were measured before and after exercise. After exercise, serum triglyceride levels significantly decreased, but no significant changes were observed in total and HDL cholesterol concentrations. Fasting glucose, insulin, and HOMA-IR levels significantly decreased after exercise, but HOMA-B-cell function did not change during the study. There was no significant difference between BMI levels before and after exercise.
From these results, it can be concluded that short-term (7 days) low-intensity physical exercise combined with hospital diet reduces serum triglycerides, insulin resistance, and fasting glucose levels without affecting BMI in non-obese Japanese type 2 diabetic patients.

Key words
Exercise · Insulin Sensitivity · Insulin Secretion · Diabetes · Triglyceride

Introduction

Type 2 diabetes is a heterogeneous disorder characterized by insulin resistance and/or defective insulin secretion [1,2]. Japanese type 2 diabetic patients are unique in that they are divided into two discrete variants: one with insulin resistance and the other with normal insulin sensitivity [3–5]. We very recently demonstrated that high body mass index (BMI), high concentrations of triglycerides and remnant-like particle cholesterol, and low HDL cholesterol level characterize Japanese type 2 diabetic patients with insulin resistance [6–8]. Furthermore, we showed that insulin resistance in non-obese Japanese type 2 diabetic patients is positively correlated with serum triglycerides levels, but not with BMI [6]. Thus, one would expect that a lowering in plasma triglycerides level could be associated with an improvement in insulin action in non-obese Japanese type 2 diabetic patients.

There are several lines of investigation suggesting that the maneuver to lower triglycerides concentrations decreases insulin resistance and fasting glucose levels in type 2 diabetic patients.

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Mingrone et al. [9] reported on two sisters with extreme hypertriglyceridemia and diabetes in whom normalization of serum triglycerides by operation improved glucose tolerance and insulin resistance. The triglyceride-lowering effects of bezafibrate [10 – 13] or clofibrate [14] have been reported to reduce insulin resistance and fasting glucose levels in type 2 diabetic patients. Paolisso et al. [15] very recently demonstrated that simvastatin and atorvastatin, a lipid lowering drug, reduce serum triglycerides, insulin resistance, and glycosylated hemoglobin levels in type 2 diabetic patients.

It is well-recognized that physical exercise *per se* lowers serum triglyceride levels in humans. Gyntelberg et al. [16] previously showed that exercise lowered triglyceride levels in patients with type IV hyperlipoproteinemia. Vanninen et al. [17] reported that physical activity improves not only triglyceride levels but also glucose tolerance in patients with type 2 diabetic patients. It is not yet known, however, whether or not the decline in triglyceride levels by physical exercise is associated with an improvement in insulin sensitivity or insulin secretion in type 2 diabetic patients.

In this context, a major issue is that not only exercise training but also body weight reduction might lower triglyceride levels and improve insulin sensitivity in type 2 diabetic patients. To separate the effects of exercise from those of weight reduction, 7 consecutive days of exercise protocol was performed in weight-stable non-obese patients during the study. Several groups have reported that 7 consecutive days of exercise training improves insulin action without changing body mass or composition [39, 43 – 45]. Another major problem is that dietary composition itself seems to have an important modulation of insulin resistance in humans [18 – 20]. High-fat diets are known to increase insulin resistance in humans [18, 19]. Feskens et al. [20] reported that fish intake is known to delay the development of diabetes in glucose-intolerant individuals. Thus, our patients were all placed in a hospital and were instructed to perform physical exercise and consume their nutritionally balanced hospital diet during the study. Therefore, the purpose of this study is to determine whether short-term (7 days) physical training could reduce serum triglyceride levels and insulin resistance in weight-stable non-obese Japanese type 2 diabetic patients.

Subjects and Methods

Thirty-nine sedentary Japanese type 2 diabetic patients participated in the study after giving their informed consent. The type 2 diabetes diagnosis was based on the WHO criteria [23]. They all had either fasting plasma glucose greater than 140 mg/dl and/or 2 h post-glucose levels greater than 200 mg/dl. None of the subjects had any physical finding suggestive of cardiovascular, pulmonary, endocrine, or renal disease, hypertension, or peripheral vascular insufficiency. Twenty of 39 patients were taking sulfonylureas, but their medication was unchanged during the course of the study. None had been receiving insulin therapy and or any medications affecting lipid metabolism. They had not consumed alcohol or performed heavy exercise for at least a week before the study. All patients were hospitalized at Kansai-Denryoku Hospital and ingested the following diet under supervision: 1,641 ± 24 (mean ± SEM) kcal/day (range1440 – 1920 kcal/day, 50 – 58 % carbohydrate, 18 – 20 % protein, and 24 – 30 % fat).

All patients engaged in exercise from 9 a. m. to 9 p. m. for 7 consecutive days. In the present study, we performed low-intensity exercise combined with walking and dumbbell exercises, since this is safe and can be managed well by the patients. They were instructed to walk at least 7000 steps and perform dumbbell exercise for 15 min twice a day, as described previously [24]. Foot count was monitored by a pedometer (Calorie Counter, Suzuken, Nagoya, Japan). During the course of the study, they walked a mean of 11 586 ± 742 steps per day. No remarkable changes were observed in pulse or blood pressure in all of the patients studied before and after exercise.

After an overnight fast, the blood was drawn from an antecubital vein for the determination of glucose, insulin and lipid profile before and 7 days after the exercise training. Plasma glucose was measured with glucose oxidase method, and serum insulin was measured using a two-site immunoradiometric assay (Insulin Riabead II, Dainabot, Japan). Coefficients of variation (CVs) were 4 % for insulin > 25 μU/ml and 7 % for insulin < 25 μU/ml, respectively. Triglyceride, total and HDL cholesterol concentrations were also measured. The low-density lipoprotein (LDL) cholesterol was calculated using the Friedewald formula [25].

Insulin action was measured with homeostasis model assessment insulin resistance index (HOMA-IR) validated against a minimal model approach [26 – 29]. It may be argued that the use of sulfonylureas in patients with diabetes might significantly affect the estimate of insulin resistance by HOMA, as these drugs are known to decrease fasting plasma glucose without substantially changing fasting plasma insulin [30]. It seems, however, unlikely, since Bonora et al. [31] and Emoto et al. [32] confirmed in the validation studies on HOMA that the correlation of insulin sensitivity estimated by such a method and that measured by the glucose clamp was not substantially different in diet-treated and sulfonylurea-treated type 2 diabetics. Therefore, we estimated HOMA-IR in diet-treated and sulfonylurea-treated diabetic patients.

Insulin secretion was calculated with the formula fasting serum insulin (μU/ml) × 20/(fasting plasma glucose [mmol/l] – 3.5) proposed by Matthews et al. [26]. We very recently showed that HOMA-B-cell function is validated against minimal model-derived insulin secretion in Japanese type 2 diabetic patients [29]. Using the hyperglycemic clamp, Stumvoll et al. [33] then disclosed that HOMA-B-cells provide an accurate estimate of B-cell function in Caucasian patients with type 2 diabetes.

Statistical analysis

Data are presented as means ± SEM. Statistical analyses were conducted using the Statview 5 system (Statview, Berkeley, CA). The means of two groups were compared with the Student's *t*-test, and $p < 0.05$ was considered as significant.

Table **1** Clinical characteristics before and after exercise

Characteristic	*Before*	*After*	*p*
BMI (kg/m^2)	23.1 ± 0.4	22.8 ± 0.4	0.343
Triglycerides (mg/dl)	149 ± 10	113 ± 7	0.004
Total cholesterol (mg/dl)	202 ± 5	190 ± 5	0.069
HDL cholesterol (mg/dl)	46 ± 2	43 ± 2	0.199
LDL cholesterol (mg/dl)	127 ± 4	125 ± 5	0.401
Fasting glucose (mg/dl)	153 ± 7	131 ± 6	0.014
Fasting insulin (μU/ml)	6.3 ± 0.4	5.0 ± 0.3	0.012
HOMA-IR	2.36 ± 0.17	1.58 ± 0.10	Approx. 0.001
HOMA-B-cell	31.6 ± 2.6	40.3 ± 5.6	0.098

Results

The subjects studied were all Japanese type 2 diabetic patients (24 men and 15 women) with an age range of 40 to 65 years (56.1 ± 1.5) and a BMI of 15.3 to 26.6 kg/m^2 (23.1 ± 0.4). They all were non-obese (BMI < 27 kg/m^2) [34]. The fasting plasma glucose and glycosylated hemoglobin (HbA1c) levels were 153 ± 7 mg/dl and 8.4 ± 0.3 %, respectively. Fasting plasma insulin levels were 6.3 ± 0.4 μU/ml. Serum triglycerides, total cholesterol, and HDL cholesterol levels were 149 ± 10 mg/dl, 202 ± 5 mg/dl, and 46 ± 2 mg/dl, respectively. Serum LDL cholesterol was 127 ± 4 mg/dl.

Table **1** demonstrates the parameters studied before and after 7 days of physical training. There was no significant difference between BMI levels before and after exercise (23.1 ± 0.4 vs. 22.8 ± 0.4 kg/m^2, P = 0.343). Serum triglyceride levels significantly fell from 149 ± 10 to 113 ± 7 mg/dl (p = 0.004). In contrast, no significant changes in total cholesterol or HDL and LDL cholesterol concentrations were observed after exercise. Plasma glucose and serum insulin levels significantly decreased from 153 ± 7 to 131 ± 6 mg/dl and 6.3 ± 0.4 to 5.0 ± 0.3 μU/ml, respectively. The HOMA-IR value was significantly lower after exercise (1.58 ± 0.10) than before exercise (2.36 ± 0.17, p < 0.001). On the other hand, there was no significant difference between HOMA-B-cell values before and after exercise.

Discussion

Exercise has long been considered in the treatment regimen for the patients with type 2 diabetes. In the present study, all patients engaged in physical exercise from 9 a.m. to 9 p.m. for 7 consecutive days. They all were non-obese, and walked a mean of 11586 steps and performed dumbbell exercise for 30 min every day. This low-intensity exercise is safe and can be easily performed by the patients, since no remarkable changes in pulse and blood pressure were observed before and 7 days after exercise. In the present study, we found that exercise combined with hospital dietary therapy improved insulin sensitivity and glucose levels but did not affect BMI level in non-obese Japanese type 2 diabetic patients. One might argue that dietary restriction *per se* improves insulin sensitivity and glucose and triglycerides concentrations in our diabetic patients. It seems, however, unlikely, as Bogardus et al. [21] and Yamanouchi et al. [22] showed that the glucose infusion rate measured by glucose clamp technique remained unchanged in the diet-only group but improved in the diet-exercise group. Gyntelberg et al. [16] previously demonstrated that exercise on approx. 4 successive days significantly reduced triglyceride levels in patients with type IV hyperlipoproteinemia, and that the triglyceride-lowering effect of exercise was not mediated by a negative caloric balance. Thus, it is conceivable that our results are mainly due to the effect of the exercise *per se* rather than to that of the dietary restriction. The beneficial effect of exercise on insulin sensitivity and glycemic control, however, is not a universal finding in type 2 diabetic patients [27 – 33]. The reason for the discrepancy in the results is not currently known.

One possible explanation for the discrepancy is the difference of the time studied. Several previous studies showing negative findings were performed in 4 – 7 days after the last bout of exercise [35 – 37]. In our present study, the blood was drawn at approx. 24 h after the last bout of exercise. The two previous reports [38, 39] in which exercise training resulted in an improvement in insulin sensitivity and glucose tolerance were studied approx. 36 h after the last exercise bout. It is well-recognized that improvements in insulin sensitivity resulting from an exercise program are mostly undetectable 3 to 5 days after the last bout of exercise [40, 41].

The second possible explanation for the discrepant results may be related to degree of the B-cell function studied, since exercise *per se* cannot substitute for the action of insulin in patients with inadequate insulin secretion. This idea is supported by a previous study showing that slight improvements in glucose tolerance were observed in type 2 diabetic patients who had marked insulin deficiency [36, 42]. In the present study, none of the patients had received or was receiving insulin therapy or had C-peptide levels greater than 0.78, suggesting that their pancreatic function was not severely impaired. However, it is important to examine the ratio of plasma proinsulin to insulin in the assessment of insulin secretion, although we did not measure plasma proinsulin level in the present study. Choi et al. [43] recently demonstrated that the elevated plasma proinsulin/insulin ratio is a marker of reduced insulin secretory capacity in healthy young men.

Of particular note is that exercise not only improved insulin sensitivity and glycemic control, but also lowered serum triglycerides level without affecting BMI. It may be argued that fat mass influenced our results, but this seems unlikely since several groups have reported that 7 consecutive days of exercise training improves insulin action without changing body mass or composition [39, 44 – 46]. Irrespective of this, our result was compatible with the previous study shown by Vanninen et al. [47] that physical activity improves both glucose tolerance and serum triglycerides level in patients with type 2 diabetes.

The mechanisms by which triglycerides are related to insulin resistance in type 2 diabetic patients are not known at present. Although insulin resistance has been suggested as the underlying defect leading to the development of endogenous hypertriglyceridemia [48], there are some study results suggesting that elevated triglyceride levels are preceding factors for the development of insulin resistance in type 2 diabetic patients [9, 49]. In families

with multiple cases of hypertriglyceridemia, increased serum triglyceride levels serve as a risk marker for subsequent development of type 2 diabetes [49]. Mingrone et al. [9] reported on two sisters with extreme hypertriglyceridemia and diabetes in whom the normalization of serum triglycerides by operation improved glucose tolerance and insulin resistance. We recently disclosed that Japanese type 2 diabetic patients with insulin resistance had significantly higher triglyceride levels compared to those with normal insulin sensitivity [6–8]. Furthermore, we showed that bezafibrate not only reduces serum triglyceride levels but also improves insulin sensitivity and glycemic control in type 2 diabetic patients [11,13]. Paolisso et al. [15] has recently demonstrated that simvastatin and atorvastatin, a lipid-lowering drug, reduces serum triglycerides, insulin resistance, and glycosylated hemoglobin levels in type 2 diabetic patients. An *in vitro* study showing that incubating IM-9 lymphocytes with very low-density lipoprotein downregulates the cell's insulin receptors [50]. Insulin binding to erythrocytes in the blood of patients with hypertriglyceridemia is reported to be low, but the improvement of hypertriglyceridemia did not correct insulin-binding abnormalities [51]. Thus, it is currently unknown whether the mechanism contributing to an enhancement in insulin sensitivity by physical exercise is the cause or the effect of the decline in serum triglycerides level in non-obese Japanese type 2 diabetic patients. Alternatively, there might be co-segregation in the response to exercise of triglycerides, glucose, and insulin sensitivity in our type 2 diabetic patients. In addition, it is important to note that peroxisome proliferator-activated receptor isoform-γ (PPARγ) controls the expression of key enzymes of lipid turnover such as the lipoprotein lipase [52], although we did not study PPARγ in the present study.

Regarding the effects of exercise on insulin secretion, we showed that low-intensity exercise did not affect insulin secretion in our patients. In this context, a major issue is that HOMA-B-cell function reflects early-phase insulin secretion to glucose only, as a positive correlation exists between HOMA-B-cell function and acute insulin response to intravenous glucose stimuli [29]. Thus, it may be considered that a glucose-lowering effect by exercise is associated with an improvement of insulin sensitivity, but not with an improvement in the early phase of insulin secretion. It is unknown, however, whether or not exercise affects endogenous insulin secretion in non-obese Japanese type 2 diabetic patients.

In summary, although our present study was performed on a limited number of patients (n = 39), it could be suggested that short-term low-intensity physical exercise (walking and dumbbell exercise) combined with diet therapy is a useful means for non-obese Japanese type 2 diabetic patients not only to lower serum triglycerides but also to improve insulin sensitivity and glucose concentration. Further studies using a large number of populations will be required to clarify the causal relationship between exercise-induced reduction in triglycerides level and an enhancement in insulin sensitivity in non-obese Japanese type 2 diabetic patients.

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