Effect of mild exercise on glycemic and bodyweight control in Japanese type 2 diabetes patients: A retrospective analysis

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Nutritional therapy, Outpatient clinic, Physical exercise

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ABSTRACT
We retrospectively evaluated the effects of mild physical exercise (P) in a routine clinical setting on glycemic and bodyweight control in Japanese type 2 diabetes patients with and without individualized nutritional therapy (D). We analyzed 49 patients who participated in P that measured 2.5 metabolic equivalents and was held once every 2 weeks, compared with 83 non-participant controls, followed over a period of approximately 1.6 years. With a Cox model, the adjusted hazard ratio for improved glycated hemoglobin by numerical count of P was 1.03 (95% confidence interval [CI] 1.00–1.07; P = 0.025). Among four categories — with neither P nor D, only P, only D, and both P and D — the hazard ratios for reduced body mass index were 1.0, 0.87 (95% CI 0.46–1.67), 0.58 (95% CI 0.25–1.30) and 2.17 (95% CI 1.03–4.59), respectively. Even mild physical exercise contributed to glycemic control. The combination of P and D exerted beneficial effects on bodyweight control.

INTRODUCTION
First-line treatment for type 2 diabetes includes nutrition and physical activity, before or in parallel with initiation of pharmacological therapy1. In terms of physical activity, it is still unclear whether mild physical exercise that might be easy for patients with type 2 diabetes to begin improves glycemic and bodyweight control. Also unclear is whether exercise interval can be effective.

Individualized nutritional therapy is associated with improved glycated hemoglobin (HbA1c), as well as reduced bodyweight in patients with type 2 diabetes2. Accordingly, such combination therapy is anticipated to lead to better control of such markers. The aim of the present study was to retrospectively evaluate the outcomes on glycemic and bodyweight control by mild long-term physical exercise once every 2 weeks in Japanese type 2 diabetes patients in a clinical setting, in both the presence and absence of individualized nutritional therapy.

METHODS
Physical exercise program
The physical exercise of the present study was initiated in the gym on site at the Iwamoto Medical Clinic, Kagawa, Japan, in September 2013 and held once every 2 weeks under the supervision of a licensed exercise therapist. The exercise period consisted of 10 min of stretching at the beginning and end, 20 min of mild individualized physical activity, and 20 min of mild individually designed bodyweight exercises. The total metabolic equivalents of physical activity in each training session was estimated at just 2–2.5, whereas the intensity was designed based on participant age, ability to move and any complications. All outpatients of the clinic were informed of the availability of this exercise program, and were free to participate and to continue free of charge.

Study patients
The study population included 49 adult type 2 diabetes outpatients at the clinic that participated in the exercise program at least once during the 4 years from September 2013 through

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August 2017. The beginning of the observation period was defined as the most recent visit before the first participation in the exercise program, and the end of the follow-up period was deemed to be the most recent visit before the end of August 2017. Also monitored were 83 type 2 diabetes outpatients who never participated in the exercise program during the same period as the controls, randomly matched at the beginning of the follow-up period for age and body mass index (BMI). Patients on dialysis, using steroid medication and/or insulin, and those using glucagon-like peptide-1 analogs or taking sodium-glucose cotransporter 2 inhibitors were excluded in advance. We defined “improved HbA1c” and “reduced BMI” as cases in which the data at the beginning of the follow-up period subtracted from those at the end were positive. The study protocol was approved by the ethics committee of the Kawasaki Medical School (No. 2803), and we released information to the public about the study on the Internet.

Measurements
Data were extracted from patient information obtained at each visit. We confirmed the total number of exercise program participations, and determined the presence or absence of individualized medical nutritional therapy for caloric restriction based on personal instruction by national registered dietitians before the beginning of the exercise program or during the observation period.

Statistical analysis
The data are expressed as mean and standard deviation. Continuous variables were compared using an age-adjusted analysis of variance (ANOVA). The associations between the categorical data were evaluated using the χ²-test. To test the significance of physical activity for improved HbA1c and reduced BMI, the Cox proportional hazards model was used, adjusted for age, sex, duration of diabetes and the dose(s) of oral hypoglycemic agent(s) as potential confounders in addition to the presence of individualized nutritional therapy. The patients were divided into tertiles based on exercise program participation number, in addition to the numerical count itself, as follows: 0 (n = 83), 1–2 (n = 27) and ≥3 times (n = 22).

Next, all participants were divided into four categories: with nutritional therapy only (D; n = 17), exercise only (P; n = 32), both (PD; n = 17) and neither (N; n = 66). To test the significance of the combined treatments, the Cox proportional hazards model adjusted with potential confounders as described above was used. The statistical analyses were carried out using the SAS software program (SAS Institute, Cary, NC, USA).

RESULTS
Table 1 shows the clinical characteristics at baseline. In the Cox proportional hazards model used in analysis including tertiles divided by the total number of participations in the exercise program, the adjusted hazard ratios for improved HbA1c by increasing tertiles were 1.0, 2.76 (95% confidence interval [CI] 0.87–8.73), and 4.17 (95% CI 1.37–12.74), respectively, and those for reduced BMI were 1.0, 1.60 (95% CI 0.86–2.98) and 0.95 (95% CI 0.44–2.07), respectively (Table 2). The adjusted hazard ratio for improved HbA1c or reduced BMI by total

| Table 1 | Clinical characteristics of patients at baseline |
|---------|-----------------------------------------------|
| Male/female (n) | With physical training | Without physical training |
| 8/41 | 31/52* |
| Individualized nutritional therapy (n) | 17 | 17 |
| Age (years) | 71.0 ± 7.5 | 69.6 ± 7.8 |
| Duration of type 2 diabetes (years) | 13.6 ± 8.7 | 13.7 ± 6.1 |
| Observation period (years) | 1.43 ± 0.33 | 1.52 ± 0.12 |
| Bodyweight (kg) | 55.4 ± 10.1 | 57.6 ± 11.6 |
| BMI (kg/m²) | 24.0 ± 4.1 | 24.0 ± 4.4 |
| HbA1c (%) | 6.40 ± 0.39 | 6.42 ± 0.61 |
| Systolic BP (mmHg) | 120.9 ± 12.2 | 124.7 ± 15.6 |
| Diastolic BP (mmHg) | 66.9 ± 12.1 | 70.0 ± 10.2 |
| AST (IU/L) | 25.5 ± 10.8 | 240. ± 8.2 |
| ALT (IU/L) | 23.2 ± 11.7 | 20.4 ± 9.7 |
| BUN (mg/dL) | 15.2 ± 4.0 | 15.7 ± 3.6 |
| Creatinine (mg/dL) | 0.58 ± 0.11 | 0.67 ± 0.24 |
| HDL-C (mg/dL) | 55.3 ± 14.5 | 57.2 ± 16.8 |
| TG (mg/dL) | 142.2 ± 72.2 | 130.2 ± 67.7 |
| LDL-C (mg/dL) | 112.7 ± 25.7 | 106.5 ± 19.4 |
| Microvascular complications (n) | | |
| Neuropathy (yes/no) | 4/45 | 18/65* |
| Retinopathy (PR/SR/NR) | 0/3/46 | 2/12/60 |
| Nephropathy (4/3/2/1) | 0/0/8/41 | 1/0/19/63 |
| Macrovascular complications (n) | | |
| Coronary/brain/PAD | 3/5/2 | 2/4/2 |
| Treatment for type 2 diabetes, hypertension and dyslipidemia (n) | | |
| DPP4 inhibitors | 29 | 48 |
| Biguanides | 12 | 28 |
| Thiazolidinediones | 1 | 5 |
| Sulfonylureas | 7 | 28 |
| Glinides | 7 | 14 |
| α-Glucosidase inhibitors | 12 | 19 |
| ARB/CCB | 16/10 | 27/22 |
| Diuretic/β-blocker | 10/4 | 2/0/6 |
| Statin/ezetimibe/β-blocker | 20/2/1 | 37/1/1 |

Data are shown as mean ± standard deviation. *P < 0.05; †P < 0.01. Body mass index (BMI) was calculated as body weight in kilograms divided by height in meters squared. The patients were diagnosed with diabetic retinopathy by ophthalmologists. Diabetic nephropathy was classified according to the classification of diabetic nephropathy 2014. Diabetic neuropathy was assessed based on the abbreviated criteria by the Diabetic Neuropathy Study Group in Japan. ALT, alanine transaminase; ARB, angiotensin II receptor blocker; AST, aspartate transaminase; BP, blood pressure; BUN, blood urea nitrogen; CCB, calcium channel blocker; DPP4 inhibitors, dipeptidyl peptidase-4 inhibitors; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NR, no retinopathy; PAD, peripheral artery disease; PR, pre- or proliferative retinopathy; SR, simple retinopathy; TG, triglyceride.
Table 2 | Adjusted hazard ratios of improved glycated hemoglobin levels and reduced body mass index according to tertiles based on total participation number in the physical exercise program as categorical data

| Total participation number(s) | 0   | 1 or 2 | ≥3   | P for trend |
|-------------------------------|-----|--------|------|------------|
| Improved HbA1c (95% CI)       | 1.0 | 2.76  | 4.17 | 0.009      |
| Reduced BMI (95% CI)          | 1.0 | 1.60  | 0.95 | 0.71       |

*P < 0.05 compared with the first tertile (0) after adjustment for age, sex, dose(s) of oral hypoglycemic agent, duration of diabetes and presence or absence of individualized nutritional therapy. BMI, body mass index; CI, confidence interval; HbA1c, glycated hemoglobin.

Table 3 | Clinical characteristics of patients at baseline

|                          | N     | P     | D     | PD    |
|--------------------------|-------|-------|-------|-------|
| Male/female (n)          | 23/43 | 4/28  | 8/9   | 4/13  |
| Age (years)              | 7.00 ± 7.2 | 7.10 ± 7.8 | 6.80 ± 10.0 | 71.1 ± 7.1 |
| Duration of type 2 diabetes (years) | 14.3 ± 5.5 | 16.0 ± 9.0 | 11.7 ± 7.9 | 90 ± 63* |
| Observation period (years) | 1.52 ± 0.13 | 1.53 ± 0.12 | 1.51 ± 0.11 | 1.25 ± 0.50* |
| Bodyweight (kg)          | 55.7 ± 10.8 | 52.6 ± 8.8 | 64.8 ± 12.0 | 60.7 ± 10.4 |
| BMI (kg/m²)              | 23.5 ± 4.0 | 22.9 ± 3.9 | 25.9 ± 4.1 | 261.1 ± 47.7 |
| HbA1c (%)                | 6.35 ± 0.62 | 6.37 ± 0.42 | 6.69 ± 0.53 | 6.46 ± 0.31 |
| Systolic BP (mmHg)       | 124.2 ± 15.8 | 120.2 ± 13.2 | 126.4 ± 15.3 | 1224.0 ± 103.3 |
| Diastolic BP (mmHg)      | 89.3 ± 9.9  | 65.2 ± 13.2 | 72.9 ± 11.0 | 702.0 ± 92.9  |
| AST (IU/L)               | 24.2 ± 8.1 | 24.3 ± 9.4 | 23.1 ± 8.7 | 278.0 ± 13.2 |
| ALT (IU/L)               | 198.8 ± 85 | 230.0 ± 122 | 22.6 ± 13.5 | 235.0 ± 11.2 |
| BUN (mg/dL)              | 15.2 ± 3.2 | 15.0 ± 3.6 | 17.6 ± 4.7 | 155.0 ± 48.7 |
| Creatinine (mg/dL)       | 0.65 ± 0.19 | 0.58 ± 0.10 | 0.73 ± 0.38* | 0.59 ± 0.13 |
| HDL-C (mg/dL)            | 57.7 ± 17.0 | 56.0 ± 15.6 | 55.5 ± 16.6 | 514.0 ± 12.5 |
| TG (mg/dL)               | 132.7 ± 69.6 | 140.8 ± 68.6 | 120.6 ± 60.8 | 1447.0 ± 80.7 |
| LDL-C (mg/dL)            | 105.7 ± 18.6 | 116.6 ± 23.4 | 109.5 ± 22.7 | 1055.0 ± 28.8 |
| Microvascular complications (n) | 16/50 | 1/31 | 2/6 | 3/14 |
| Retinopathy (yes/no)     | 2/10/54 | 0/2/30 | 0/2/6 | 0/1/16 |
| Nephropathy (4/3/2/1)    | 0/0/13/53 | 0/0/2/30 | 1/0/6/10 | 0/0/6/11 |
| Macrovascular complications (n) | 2/3/2 | 0/4/0 | 0/1/0 | 3/1/2 |
| Treatment for type 2 diabetes, hypertension and dyslipidemia (n) |  |  |  |  |
| DPP4 inhibitors          | 37    | 21    | 11   | 8    |
| Biguanides               | 18    | 7     | 10   | 5    |
| Thiazolidinediones       | 4     | 1     | 1    | 0    |
| Sulfonylureas            | 23    | 6     | 5    | 1    |
| Glinides                 | 9     | 6     | 5    | 1    |
| α-glucosidase inhibitors | 16    | 12    | 3    | 0    |
| ARB/CCB                  | 22/6  | 9/5   | 5/6  | 7/5  |
| Statin/ezetimibe/fibrate | 30/1/1 | 14/0/1 | 7/0/0 | 6/2/0 |

Data are shown as mean ± standard deviation. Based on the presence and absence of individualized nutritional therapy and physical exercise, all participants were divided into four categories: with both (PD), nutritional therapy only (D), physical exercise only (P) and neither (N). *P < 0.05 vs category N; †P < 0.05 vs category P. Body mass index (BMI) was calculated as bodyweight in kilograms divided by height in meters squared. The patients were diagnosed with diabetic retinopathy by ophthalmologists. Diabetic nephropathy was classified according to the classification of diabetic nephropathy 2014. Diabetic neuropathy was assessed based on the abbreviated criteria by the Diabetic Neuropathy Study Group in Japan. ALT, alanine transaminase; ARB, angiotensin II receptor blocker; AST, aspartate transaminase; BP, blood pressure; BUN, blood urea nitrogen; CCB, calcium channel blocker; DPP4 inhibitors, dipeptidyl peptidase-4 inhibitors; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NR, no retinopathy; PAD, peripheral artery disease; PR, pre- or proliferative retinopathy; SR, simple retinopathy; TG, triglyceride.

participation number in the exercise program was 1.03 (95% CI 1.00–1.07; P = 0.025) and 1.01 (95% CI 0.99–1.03; P = 0.44), respectively.

Table 3 shows the clinical characteristics at baseline according to four categories. In the Cox proportional hazards model used in analysis including the four categories (N, P, D and...
PD), the adjusted hazard ratios for improved HbA1c were 1.0, 3.40 (95% CI 0.86–13.47), 2.88 (95% CI 0.74–11.21) and 9.69 (95% CI 2.59–36.00), respectively. Similarly, the adjusted hazard ratios for reduced BMI were 1.0, 0.87 (95% CI 0.46–1.67), 0.58 (95% CI 0.25–1.30) and 2.17 (95% CI 1.03–4.59), respectively (Table 4).

During observation, numbers of different types and doses of oral hypoglycemic agents did not statistically change between the beginning and the end in each group, or between the two groups.

DISCUSSION

In the present observational retrospective study of Japanese type 2 diabetes patients, we found that mild exercise, even if its interval was only once every 2 weeks, improved HbA1c not BMI, but that both improvements were obtained when such mild exercise was added to an individualized nutritional therapy program.

We found that the adjusted hazard ratio for improved HbA1c by total participation number was significant. In addition, categorized analysis showed that participation of three times or more significantly improved HbA1c levels when compared with the category of non-participation. The results might indicate that patients who participated in the exercise program even only a few times were motivated by the trainer’s instruction, and tried to adopt and continue such exercise in their own daily lives despite a relatively low participation number in the exercise program, but we did not evaluate patients’ daily exercise or direct relationship between exercise and HbA1c or BMI.

Combined with individualized nutritional therapy, the quality and quantity of physical exercise in the present study might have been sufficient for both outcomes. Several previous studies showed the importance of diet therapy to enhance physical therapy for glucose and bodyweight control. These results support the idea that continuous lifestyle management regarding both diet and exercise is recommended, even if the exercise regimen is relatively mild.

The present study had several limitations. First, it was a retrospective observational study with a limited study population, leading to a selection bias, because participants of exercise or nutritional therapy might have been interested in participation. Second, the number of patients undergoing the individualized nutritional therapy was also limited. Finally, we evaluated the effect of exercise by comparing changes in HbA1c and BMI at the beginning and end of the observation period only. In addition, patients attending the exercise program were predominantly women.

In conclusion, a combination of individualized nutritional therapy and mild exercise exerted marked beneficial effects on glycemic and bodyweight control in the present study, although further prospective study is necessary to confirm these findings.

DISCLOSURE

SN has received honoraria for lectures from Sanofi. HK has received honoraria for lectures and scholarship grants from Sanofi, Novo Nordisk, Lilly, Boehringer Ingelheim, MSD, Takeda, Ono Pharma, Daiichi Sankyo, Sumitomo Dainippon Pharma, Mitsubishi Tanabe Pharma, Pfizer, Kissei Pharma, AstraZeneca, Astellas, Novartis, Kowa, Chugai, and Taisho Pharma. KK has been an advisor to, received honoraria for lectures from and received scholarship grants from Novo Nordisk Pharma, Sanwa Kagaku Kenkyusho, Takeda, Taisho Pharmaceutical Co., Ltd, MSD, Kowa, Sumitomo Dainippon Pharma, Novartis, Mitsubishi Tanabe Pharma, AstraZeneca, Nippon Boehringer Ingelheim, Chugai, Daiichi Sankyo, and Sanofi. MI has received honoraria for lectures from Sanofi and for clinical trials from Kissei Pharma and Boehringer Ingelheim.

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