

The Effect of Insulin Resistance Improvement Due to Lifestyle Intervention on Overweight Perimenopausal Japanese Women: A Preliminary Study

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Abstract

Objective: We hypothesized that body composition and biomarkers of menopausal obesity would be affected by administration of a nutrition and exercise regimen. To test this hypothesis, an interventional study was performed in which perimenopausal subjects increased their daily level of physical activity and decreased their daily caloric intake for a period of 12 weeks.

Method: Nine patients with a chief complaint of obesity and menopausal disorders were enrolled in this study. We prescribed that the subjects engage in the daily physical activity of walking more than 10,000 steps, which is equivalent to 150 to 400 kcal per day, and reduce their daily nutritional intake by 200 kcal. Daily physical activity was measured with a computerized accelerometer, and nutrition intake was measured using food frequency questionnaires. Body composition was measured via biophysical impedance analysis. Biochemical examinations were performed before and after the study. As an assessment of glucose tolerance, homeostasis model assessment-insulin resistance (HOMA-IR) values were measured.

Results: There were no significant changes in weight, body mass index, or body composition after 12 weeks. However, daily physical activity related to energy consumption was slightly but not significantly increased. Six of the nine subjects (66.7%) had abnormal baseline HOMA-IR values (mean 7.0 ± 2.6 ; normal upper limit = 1.5) and demonstrated decreases in HOMA-IR values, with an average of 5.2 ± 2.3 ($P < 0.05$), after 12 weeks of study.

Conclusion: Our mild intervention on daily physical activity and nutrition changed HOMA-IR values, an assessment of impaired glucose tolerance. These results suggest that longitudinal mild intervention on daily physical activity and nutrition could change insulin sensitivity even without weight reduction.

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Key words: menopause, obesity, metabolic syndrome, physical activity, body composition

Introduction

Obesity tends to occur in the perimenopausal period owing to changes in lipid and glucose metabolism accompanied by ovary hypoactivity^{1,2} and decreased physical activity due to age-related factors^{3,4}. Despite Japan's having the longest life expectancies in the world, the contribution of lifestyle-related diseases to overall morbidity has been increasing⁵. Lifestyle-related diseases, such as diabetes mellitus, hyperlipidemia, high blood pressure, and obesity, are the main risk factors for metabolic syndrome^{6,7}. Insulin resistance is a basic sign of metabolic syndrome, and obesity is the most fundamental factor causing insulin resistance⁸. In 2002, the Japanese government performed a survey of patients with diabetes mellitus. About 7.4 million people were highly suspected to have diabetes mellitus and another 8.8 million people possibly had diabetes mellitus. It was presumed that the numbers in both groups are increasing rapidly, especially in women. Increased physical activity and decreased nutritional intake are important factors in treating obesity in order to prevent lifestyle-related diseases and metabolic syndrome⁹. In 2000, the Ministry of Health, Labor and Welfare of Japan proposed a National Health Initiative in the 21st century ("Health Japan 21") that sets forth objectives to be achieved by the year 2010⁵. The government's proposed initiative stated that in order to prevent lifestyle-related diseases, an increase in the amount of daily physical activity and appropriate nutrition are needed to improve health⁵.

We hypothesized that daily physical activity, body composition and biomarkers related to obesity would show improvement by carrying out a suitable nutritional and exercise prescription tailored to the patient's health status. As a preliminary study to test this hypothesis, we performed the present interventional study in which we asked overweight perimenopausal women to increase walking activity without requiring a special time for exercise for a period of 12 weeks. Changes in daily physical activity, body composition and obesity-related

biomarkers were investigated before and after the intervention.

Materials and Methods

Subjects

From June through September 2004, 9 patients with a chief complaint of obesity and menopausal disorders were enrolled in this study. In accordance with university and hospital regulations for human research, informed consent was obtained before subjects were enrolled. All subjects were asked to volunteer when they were seen as outpatients for treatment of menopausal disorders. Patients with neurological, metabolic, or endocrinological diseases such as diabetes mellitus, hyperthyroidism, and heart complications, were excluded from the study.

Measurements

Daily physical activity: Daily physical activity was measured with a computerized accelerometer (Lifecorder EX; Suzuken, Nagoya, Japan) and associated software (Lifelyzer 02 Pro; Suzuken). Steps and accelerations were recorded at 4-second intervals, and acceleration data were categorized into 11 physical activity levels (level 0, 0.5, and 1 to 9). The accelerometer reported the time spent in each physical activity level per day. A strong correlation was shown between the activity levels detected by the accelerometer and the metabolic equivalents (METs). The quadratic equation regression is as follows¹⁰:

$$\text{METs} = 0.043 \times (\text{activity level})^2 + 0.379 \times (\text{activity level}) + 1.361. \quad (1)$$

Levels 0 and 0.5 were ruled out of this equation, so the lowest MET value of 1 was given to these levels. The mean daily physical activity was calculated using the following equation.

$$\begin{aligned} & [|\text{level 0 (METs)} \times \text{level 0 (Time)}| + |\text{level 0.5 (METs)} \times \text{level 0.5 (Time)}| + \dots \\ & + |\text{level 9 (METs)} \times \text{level 9 (Time)}|] / 1.440 \quad (2) \end{aligned}$$

The standard MET value is equal to 3.5 mL of oxygen consumption per kilogram body weight per minute. The metabolism of 1 L of oxygen results in production of 4.85 kcal of heat, so to estimate energy

consumption, the following equation was used:

$$\text{Energy consumption (Kcal)} = \text{METs} \times 3.5 \times \text{body weight} \times 4.85/1,000 \times \text{Time (min)} \quad (3)$$

The daily physical activity related to energy consumption was calculated using the following equation:

$$\text{Daily physical activity related to energy consumption} = \text{level } 0_{\text{EC}} + \text{level } 0.5_{\text{EC}} + \dots + \text{level } 9_{\text{EC}}. \quad (4)$$

Nutrition intake: Nutritional intake was measured with food frequency questionnaire (FFQ) software (Chatty, Total Software Corporation, Kagoshima, Japan). The software provides 40 interviewer-administered semiquantified food habit questions which include 18 food groups with 92 food items. For each item on the food list, subjects were asked to estimate the frequency of consumption based on specified frequency categories that indicate the number of times the food is usually consumed per month as well as the calculated protein, fat, and carbohydrate energy ratios. When food intervention studies were performed, the validity of food frequency questionnaires was recognized by screening each subject's eating habits and assessing the diet during the study^{11,12}.

Body composition: Body composition was measured with a body composition analyzer (InBody³²; Biospace, Seoul, Republic of Korea) using the biophysical impedance analysis method. InBody³² used 8-point tactile electrodes and multifrequency (5, 50, 250, and 500 kHz) analysis to measure body weight, total body water (intracellular and extracellular fluid), fat mass, muscles, and fat free mass¹³.

Biochemical examinations: Biochemical examinations, consisting of measurements of blood glucose, insulin, hemoglobin A1c (HbA1c), low-density lipoprotein (LDL)-cholesterol, high-density lipoprotein (HDL)-cholesterol, triglycerides, leptin, and adiponectin, were performed before and after the study. Plasma levels of leptin and adiponectin were measured by radioimmunoassay¹⁴ and by enzyme-linked immunosorbent assay¹⁵, respectively. As an assessment of impaired glucose tolerance, homeostasis of minimal assessment of insulin resistance (HOMA-IR) was employed. HOMA-IR was

calculated using the following equation¹⁶:

$$\text{fasting plasma glucose (mg/dL)} \times \text{fasting insulin } (\mu\text{U/mL})/405 \quad (5)$$

It has been reported that HOMA-IR is highly correlated with insulin sensitivity during euglycemic clamping¹⁷.

Experimental Procedure

The duration of this study was 12 weeks. Lifestyle assessments consisting of monitoring of daily physical activity, measurement of body composition, and interview of FFQ's were performed before the first nutritional and fitness prescription. These lifestyle assessments were then performed every 4 weeks.

Intervention for the subjects began after the first lifestyle assessment. Subjects received 60-minute counseling sessions to educate them in regards to the nutritional and fitness prescription. Additional counseling sessions were given to subjects every 4 weeks following the lifestyle assessments. As a goal for subjects, a 2-kg/m² reduction in body mass index (BMI) was set. To achieve this goal we prescribed that the subjects take more than 10,000 steps of daily physical activity, which is equivalent to 150 to 400 kcal per day¹⁸ and reduce their daily nutritional intake by 200 kcal. We assumed that a 2-kg/m² decrement of BMI would result in a 3,000-g reduction in fat. Since 1 g of fat has 9 kcal, it was necessary to consume 27,000 kcal or more over the 12 weeks of study, or 320 kcal or more per day. The average amount of daily energy consumption related to physical activity of people with typical work habits is about 200 to 300 kcal. We converted that by raising daily energy consumption to 400 kcal, and also reducing 200 kcal of nutritional intake per day, resulting in a calorie reduction of 300 kcal or more per day. We recommended an exercise activity level of about 50% VO₂Max¹⁹, a level equivalent to 5 to 6 METs when walking with quick steps. An exercise level of 50% VO₂Max was calculated from the following equation²⁰:

$$\begin{aligned} &50\% \text{ VO}_2\text{Max heart rate} \\ &= \{ (220 - \text{age}) - \text{resting heart rate} \} \times 0.5 + \\ &\quad \text{resting heart rate} \quad (6) \end{aligned}$$

If the heart rate reaches this level, the physical

activity is equivalent to 50% VO₂Max.

Statistical Analysis

Values are presented as means \pm standard error (SE). Comparisons of measurements from before and after the study were performed with the paired *t*-test. Differences were considered significant with a probability value of <0.05 .

Result

Table 1 shows changes in characteristics before and after the study. There were no significant changes in weight, BMI, total body water, fat mass, or fat-free mass throughout the study.

The daily number of steps was $10,090 \pm 960$ at baseline and had increased to $10,649 \pm 889$ after 12 weeks. The change in the number of steps was not significant. Daily energy consumption was $1,879 \pm 110$ (kcal/day) at baseline and had increased to $1,907 \pm 134$ (kcal/day) after 12 weeks. The increase

in energy consumption was also not statistically significant.

Table 2 shows the nutritional intake of subjects before and after the study. After 12 weeks of study, total energy intake, fat intake per day, and fat energy ratio tended to be decreased compared with baseline, but the differences were not significant.

Table 3 shows the biochemical variables of all subjects. No values had changed significantly.

Five of 9 subjects showed decreases in weight (1.2 ± 0.4 kg), total body water (0.5 ± 0.3 L), fat mass (0.7 ± 0.3 kg), and fat free mass (0.5 ± 0.2 kg). There were no significant changes in the daily number of steps, daily physical activity related to energy consumption, nutrition, or biochemical variables between the 5 weight-decreased subjects and the other subjects.

Six of 9 subjects (66.7%) had abnormal baseline HOMA-IR values (cut off <1.5), and 5 subjects showed improved values after 12 weeks of study. **Table 4** shows the changes in physical characteristics, nutritional intake, biochemical variables, and glucose metabolism of subjects with abnormal HOMA-IR results. After 12 weeks of study, insulin and HOMA-IR values were decreased significantly compared with baseline. Three of 5 subjects with abnormal baseline HOMA-IR values that improved during the study also showed decreases in weight.

Figure 1 shows correlations between HOMA-IR with adiponectin before and after the experiment for the 5 subjects with abnormal baseline HOMA-IR values who showed improvement after 12 weeks of study. HOMA-IR values had a tendency to correlate

Table 1 Age and physical characteristics of subjects

Characteristics	Baseline (n=9)	12 weeks (n=9)
Age (y)*	54.1 ± 3.8	
Height (m)*	1.54 ± 0.03	
Weight (kg)*	67.3 ± 5.5	67.2 ± 5.8
BMI (kg/m ²)*	28.1 ± 1.8	28.1 ± 1.9
Total body water (L)*	31.9 ± 2.2	31.6 ± 2.2
Fat mass (kg)*	24.9 ± 2.9	24.7 ± 3.2
Fat-free mass (kg)*	42.5 ± 2.9	42.5 ± 3.0

* Values are given as mean \pm SE.

Table 2 Nutritional change of subjects

	Baseline (n=9)	12 weeks (n=9)
Total energy intake (kcal/day)*	$1,696.7 \pm 149.9$	$1,654.6 \pm 106.7$
Protein (g/day)*	56.5 ± 5.8	56.7 ± 4.4
Fat (g/day)*	47.4 ± 4.9	45.1 ± 3.5
Protein energy ratio (%)*	13.1 ± 0.6	13.7 ± 0.5
Fat energy ratio (%)*	25.6 ± 1.6	24.7 ± 1.8
Carbohydrate energy ratio (%)*	61.3 ± 1.5	61.5 ± 2.0

* Values are given as mean \pm SE.

Table 3 Biochemical examinations change of subjects

	Baseline (n=9)	12 weeks (n=9)
Total cholesterol (mg/dL)*	190.0 ± 7.9	203.3 ± 8.5
LDL [†] cholesterol (mg/dL)*	109.3 ± 6.4	118.9 ± 6.7
HDL [‡] cholesterol (mg/dL)*	57.8 ± 3.6	61.2 ± 3.3
Triglyceride (mg/dL)*	163.9 ± 31.3	148.7 ± 40.7
HbA1c§ (%)*	5.1 ± 0.1	5.2 ± 0.1
Insulin (μg/mL)*	17.8 ± 6.6	14.1 ± 5.2
Glucose (mg/dL)*	104.3 ± 6.0	107.1 ± 3.4
HOMA-IR *	5.0 ± 1.9	4.0 ± 1.6
Leptin (ng/mL)*	15.9 ± 3.7	15.9 ± 4.6
Adiponectin (μg/mL)*	9.9 ± 1.5	9.9 ± 1.7

* Values are given as mean ± SE, [†]LDL; low-density lipoprotein, [‡]HDL; high-density lipoprotein, §HbA1c; hemoglobin A1c, || HOMA-IR; homeostasis model assessment-insulin resistance.

Table 4 Changes of physical characteristics, nutrition, biochemical examinations and glucose metabolism of subjects with abnormal HOMA-IR results

	Baseline	12 weeks	p
Weight (kg)*	65.4 ± 6.0	65.7 ± 6.4	N.S.
Total body water (L)*	30.1 ± 2.1	30.2 ± 2.3	N.S.
Fat mass (kg)*	25.3 ± 3.3	25.3 ± 3.5	N.S.
Fat free mass (kg)*	40.2 ± 2.8	40.5 ± 3.0	N.S.
Total energy intake (kcal/day)*	1,690 ± 218	1,620 ± 159	N.S.
Protein energy ratio (%)*	13.6 ± 0.8	13.5 ± 0.7	N.S.
Fat energy ratio (%)*	26.7 ± 2.3	25.3 ± 2.7	N.S.
Carbohydrate energy ratio (%)*	59.7 ± 2.0	61.2 ± 2.9	N.S.
Total cholesterol (mg/dL)*	195.5 ± 9.6	202.7 ± 11.2	N.S.
LDL cholesterol (mg/dL)*	113.5 ± 7.2	116.2 ± 6.3	N.S.
HDL cholesterol (mg/dL)*	56.7 ± 5.5	59.0 ± 4.7	N.S.
Triglyceride (mg/dL)*	204.3 ± 35.6	187.7 ± 54.4	N.S.
HbA1c (%)*	5.1 ± 0.2	5.3 ± 0.2	N.S.
Insulin (μg/mL)*	24.6 ± 8.8	18.1 ± 7.4	< 0.05
Glucose (mg/dL)*	110.0 ± 8.0	107.7 ± 4.6	N.S.
HOMA-IR*	7.0 ± 2.6	5.2 ± 2.3	< 0.05
Leptin (ng/mL)*	18.2 ± 5.4	18.8 ± 6.8	N.S.
Adiponectin (μg/mL)*	10.7 ± 2.2	10.6 ± 2.5	N.S.

* Values are given as mean ± SE.

negatively with plasma adiponectin levels before and after the experiment, but the correlation was not significant.

Figure 2 shows the mean daily physical activity of

5 subjects with abnormal baseline HOMA-IR values. The mean daily physical activity was slightly increased (0.02 METs) during experiment, but the change was not significant.

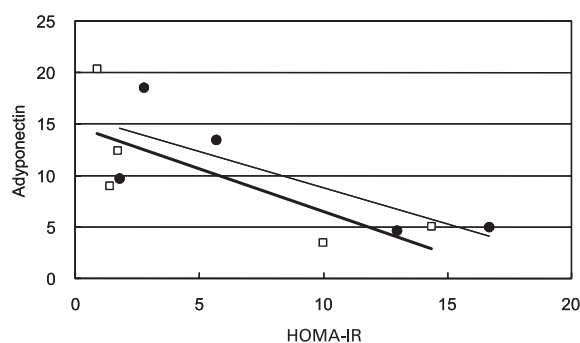


Fig. 1 Linear correlation analysis of HOMA-IR and adiponectin in 5 subjects with abnormal baseline HOMA-IR values before and after the 12 weeks of study. HOMA-IR values were correlated with plasma adiponectin levels before (closed circle and thin line, $y = -0.70x + 15.883$, $r = 0.78$) and after (open box and thick line, $y = -0.83x + 14.785$, $r^2 = 0.76$) the experiment.

Discussion

In the present study, two principle findings were obtained. The first is that a high percentage (66.7%) of overweight perimenopausal women had abnormal baseline HOMA-IR values, which indicate insulin sensitivity. The second finding is that the abnormal insulin sensitivity was improved after 12 weeks of study without decreases in body weight or increases in daily physical activity.

The first finding is largely in agreement with results of earlier studies that found that postmenopausal women have reduced insulin sensitivity resulting from postmenopausal hypoestrogenis^{1,2} and the increased risk of developing central obesity and insulin resistance following menopause in women of Japanese ethnicity^{21,22}. However, the second finding disagrees with those of earlier studies. Earlier studies have shown that appropriate dietary restriction and moderate increases in daily physical activity improved individual insulin sensitivity with weight reduction during the study^{23,24}. In addition, other studies have shown that increased physical activity improves individual insulin sensitivity in obese patients²⁵ and in nonobese patients²⁶ without reductions in weight. The question arises as to the reason why individual insulin sensitivity was

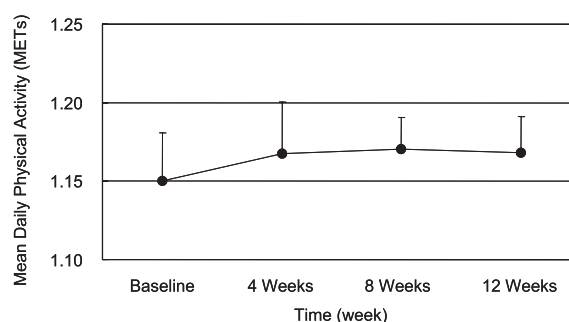


Fig. 2 The mean daily physical activity of five abnormal HOMA-IR subjects during 12 weeks of study. The mean daily physical activity was slightly increased during the experiment.

improved in the present study without weight reduction or increased physical activity. One possible reason is the effect of long-term physical exercise. Continued physical exercise reduces peripheral tissue sensitivity to insulin in patients with impaired glucose tolerance and type 2 diabetes mellitus²⁷. Some reports have shown that exercise enhances skeletal muscle glucose uptake. The activity of the glucose transporter 4 (GLUT 4), responsible for glucose transport from blood to muscle tissue, is increased, resulting in improved glucose tolerance and prevention of diabetes mellitus²⁸. Another possible reason for improved insulin sensitivity is the acute effects of exercise. Exercise provokes the release of insulin-counterregulating hormones, such as glucagon and catecholamine, which ultimately cause a reduction in insulin activity²⁹. Only 7 to 10 days of aerobic exercise are required to improve insulin sensitivity in hypertensive women³⁰ and in obese men³¹. Together with this data, the data shown in **Figure 2** suggest that mild and longitudinal exercise, an increase in mean daily physical activity of only 0.02 MET over 12 weeks, which is not burdensome to daily life, has a favorable effect on insulin sensitivity.

Leptin and adiponectin, which are biomarkers of lipid metabolism and obesity, were examined in the present study. That the levels of these biomarkers did not change significantly is in agreement with previous studies. Hellenius et al. have shown in a study of physical activity and nutrition prescriptions in 158 subjects with hyperlipidemia that there were

no favorable effects on lipid metabolism³². Plasma leptin levels were positively correlated with BMI and body fat³³ and decreased in both obese and nonobese subjects following aerobic exercise and personal diet counseling³⁴. Hotta et al. have shown that plasma adiponectin levels are highly correlated with whole-body insulin sensitivity, as measured with the insulin clamp method, in both monkeys and humans³⁵. In the present study, HOMA-IR values, which were abnormal before the study, were correlated with plasma adiponectin levels, and the linear regression slope was decreased from -0.70 to -0.83 . This left and downward shift suggests a favorable change in adiponectin and HOMA-IR in response to nutrition and exercise therapy.

Our lifestyle intervention program did not result in significant changes in the physique or biomarkers of subjects. Was it necessary to further increase exercise load and to manage nutritional intake more strictly in attain a benefit? Stewart et al. have performed a randomized controlled study to investigate changes in factors of metabolic syndrome by moderate exercise in 104 subjects aged 55 to 75 years³⁶. Changes in blood pressure and levels of lipids, lipoproteins, insulin, and glucose were compared between subjects who performed 60 minutes of exercise 3 times per week and subjects who received a booklet that encouraged an increase in exercise. Metabolic syndrome decreased 41% in the exercise group but decreased only 18% in the control group. That is, for an exercise program to work effectively, adherence is important. From a long-term viewpoint, significant and abrupt increases in exercise load and strict management of nutritional intake may not be of benefit because the increased burden may not be sustainable. To strengthen the motivation for continued participation in an exercise program, it may be helpful to increase the frequency of counseling and lifestyle assessments.

In conclusion, insulin sensitivity in overweight premenopausal women was improved during this interventional study. The results support earlier work showing that fitness and nutritional intervention induce favorable changes in glucose metabolism. Asian people are especially prone to diabetes mellitus and cardiovascular disease even if

they are only mildly overweight²¹. Both Japanese and American government organizations for health have stated that to prevent lifestyle-related diseases, an increase in the amount of daily physical activity is more effective than attempting to improve health through intentional exercise^{5,18}. These earlier studies and government recommendations, together with the present study, suggest that an early lifestyle intervention is necessary to prevent lifestyle-related diseases in overweight perimenopausal women.

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