Insulin-Sensitizing Effects of Exercise on Adiponectin and Retinol-Binding Protein-4 Concentrations in Young and Middle-Aged Women

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Context: Exercise training enhances insulin sensitivity. Changes in retinol-binding protein-4 (RBP4) and adiponectin levels are linked to insulin resistance.

Objective: We tested whether the insulin-sensitizing effect of exercise is associated with age-related changes in circulating RBP4 and adiponectin levels in women.

Design, Subjects, and Intervention: We studied 36 healthy young (22.4 ± 2.8 yr) and 38 middle-aged (59.8 ± 5.9 yr) women. All subjects performed 60 min of aerobic exercise three times per week for 10 wk at about 70% maximal exercise capacity.

Results: After a 10-wk training program, maximal exercise capacity was significantly increased in both young and middle-aged women, suggesting increased oxidative capacity. Insulin sensitivity was also improved, as indicated by decreases in plasma insulin levels and homeostasis model assessment for insulin resistance index. Serum adiponectin and RBP4 concentrations were increased and decreased more in older than younger women, respectively ($P < 0.01$). Concurrently, circulating transthyretin levels were also decreased in older subjects in response to exercise training. The older women showed higher correlations between changes in adiponectin or RBP4 levels and obesity indices or metabolic parameters than the younger group. When subjects showing increasing adiponectin or decreasing RBP4 levels were classified as responders, there were higher correlations between these changes in responders than in nonresponders.

Conclusions: We conclude that the mechanism for the insulin-sensitizing effects of exercise could involve increased adiponectin and reduced RBP4 levels in exercise-trained women. These data suggest that alterations in circulating RBP4 and adiponectin levels could play an important role in regulating insulin sensitivity. **(*J Clin Endocrinol Metab* 93: 2263–2268, 2008)**

Exercise has been known to increase insulin sensitivity in people both with and without diabetes (1, 2). According to several large-scale and prospective studies, higher levels of physical activity are known to be associated with fewer cardiovascular disease events (3, 4).

Retinol-binding protein-4 (RBP4) is a newly discovered fat-derived adipokine that specifically binds to retinol (5) and transthyretin (TTR) (6–8). RBP4 has been reported to provide a link between obesity and insulin resistance in mice and humans (9, 10). In fact, elevated serum RBP4 levels were associated with the components of metabolic syndrome in insulin-resistant subjects (11, 12). Recent studies demonstrated that serum TTR levels were increased in obese subjects and subjects with impaired glucose tolerance/type 2 diabetes, and its levels were higher in visceral *vs.* sc obesity (6). However, some studies reported that serum RBP4 levels were not elevated in obese elderly women, and

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Abbreviations: AUC, Area under the curve; BMI, body mass index; FPG, fasting plasma glucose; FPI, fasting plasma insulin; HDL, high-density lipoprotein; HOMA, homeostasis model assessment; HOMA-β, HOMA for pancreatic β-cell function; HOMA-IR, HOMA for insulin resistance; LDL, low-density lipoprotein; OGTT, oral glucose tolerance test; RBP4, retinol-binding protein-4; TTR, transthyretin; VO_2max, maximal exercise capacity; WC, waist circumference.

RBP4 mRNA level was not related to insulin sensitivity (13, 14). It is therefore unclear whether elevated RBP4 levels contribute to the pathogenesis of insulin resistance and abnormal glucose metabolism at this time.

Adiponectin has attracted considerable attention recently as an adipokine that may have critical roles in the development of atherosclerosis (15). Importantly, low adiponectin levels are a risk factor for the subsequent development of diabetes and cardiovascular diseases (16–18). Although several studies have examined the effects of exercise on circulating adiponectin concentrations, the results were inconclusive (19–21). Only one study demonstrated that the RBP4 level was decreased in response to 4 wk of exercise training in a wide age range of subjects (12). However, regulation of RBP4 and TTR by exercise in young and old women has not been investigated.

In the current study, we investigated whether exercise could alter circulating RBP4, TTR, and adiponectin levels and whether these changes would impact whole-body glucose metabolism in young and middle-aged women. Furthermore, we evaluated whether the insulin-sensitizing effects of exercise are associated with the metabolic parameters of insulin resistance.

Subjects and Methods

Subjects

A total of 132 healthy volunteers (mean age 42.1 yr) were recruited from women visiting a fitness center. We excluded subjects who had metabolic or cardiovascular diseases. Smokers, ex-smokers, and subjects who were on any specific diet program were also excluded. Finally, we recruited 36 healthy young women aged 18–29 yr (younger group) and 38 healthy older women aged 50–71 yr (older group). All subjects participated in the study voluntarily, and informed consent was obtained. The study protocol was approved by Seoul National University Hospital Ethics Committee.

Exercise program

All subjects underwent a supervised aerobic exercise program that consisted of three sessions a week for 10 wk, 1 h per session, aiming for 60–80% of their maximal exercise capacity (VO_2max). The percentage of attendance for all subjects was 95%. VO_2max was determined by a stepwise exercise protocol on a bicycle ergometer (Combi, Tokyo, Japan) with the subjects in the sitting position. The stepping exercise was composed of three levels of load every 4 min, after which the load was increased by 15–20 W/min until volitional exhaustion. Expired gas was collected in a Douglas bag, and oxygen and carbon dioxide contents were analyzed with an expired-gas monitor (model 1H2A; San-Ei, Tokyo, Japan).

Anthropometric and biochemical parameters

Height, weight, waist circumference (WC), and blood pressure were measured by standard methods. Participants were asked to refrain from consuming alcohol for 7 d and to fast overnight for 8–14 h before blood sampling. Plasma was separated immediately by centrifugation (2000 rpm for 20 min at 4 C), and biochemical assays were performed immediately. Fasting plasma glucose (FPG) and lipids were measured enzymatically (Hitachi, Tokyo, Japan). Fasting plasma insulin (FPI) concentration was determined by RIA (Linco, St. Charles, MO).

All participants underwent a 2-h, 75-g oral glucose tolerance test (OGTT) at baseline and after 10 wk of exercise training. Plasma glucose concentrations were measured before and 30, 60, 90, and 120 min after the ingestion of a 75-g glucose solution. The total integrated glucose response was quantified by calculating the area under the curve of glucose ($AUC_{glucose}$). The homeostasis model assessment (HOMA) was used for the assessment of pancreatic β-cell function (HOMA-β) and insulin resistance (HOMA-IR) (22).

Measurement of RBP4, TTR, and adiponectin

RBP4 level was measured by an ELISA using a polyclonal antihuman RBP4 antibody. The intraassay precision of the ELISA system in terms of coefficient of variance was between 4 and 8%, and it was between 5 and 10% between assays. TTR levels were measured by Western blotting (polyclonal rabbit antihuman TTR IgG; DakoCytomation, Hamburg, Germany). Absorbance was measured at 595 nm by use of spectrophotometer (Microplate Reader; Bio-Rad, Munich, Germany). The interassay coefficient of variation was 5–10%. Adiponectin level was measured using ELISA (Adipogen; Adipogen Inc., Seoul, Korea).

Statistics

All data are presented as the mean ± SD. Student's *t* test to compare variables between the groups and paired *t tests* to analyze changes of parameters before and after exercise were used. Pearson's correlation was used to analyze various parameters and changes in parameters The Kolmogorov-Smirnov goodness-of-fit test was used to confirm the normal distribution of factors (Kolmogorov-Smirnov Z = 0.686, 1.242, 1.165, and 0.811 in VO_2max, adiponectin, RBP4, and HOMA-IR, respectively; all $P > 0.05$). $P < 0.05$ was considered statistically significant by using SPSS Windows version 11.0 (Chicago, IL).

Results

Baseline characteristics

The body mass index (BMI) and WC of the older group were greater than that of the younger group. The older group also had higher baseline levels of blood pressure, FPI, total and low-density lipoprotein (LDL)-cholesterol, triglyceride, and HOMA-IR than the younger group but lower levels of high-density lipoprotein (HDL)-cholesterol (Table 1). In the OGTT, there were no subjects with diabetes, but three of younger group and three of older group were classified into impaired fasting glucose. Two of the older group were classified with impaired glucose tolerance.

Changes in physiological and biochemical parameters before and after exercise

In both groups, VO_2max, insulin resistance parameters, and adiponectin concentration increased significantly after exercise training. However, obesity indices and RBP4 concentration decreased significantly in the older group but not in the younger group (Table 1). We divided subjects into two groups according to their individual response of adiponectin or RBP4 by exercise: adiponectin responders, defined when they showed increased adiponectin, and RBP4 responders, when they showed decreased RBP4. Finally, adiponectin concentrations were increased in 24 of 36 younger (67%) and 29 of 38 older subjects (76%, adiponectin responders), and RBP4 levels were decreased in 18 of 36 younger (50%) and 29 of 38 older participants (76%, RBP4 responders).

In the comparison by response of adiponectin, indices related to obesity and insulin resistance including body weight, BMI, and HOMA-IR were more decreased in responders than nonresponders ($P < 0.05$). Similarly, these factors were more de-

TABLE 1. Changes in anthropometric and biochemical parameters after 10-wk training program in the younger and older groups of women

	Younger		Older	
	Before exercise	After exercise	Before exercise	After exercise
Age (yr, range)	22.4 ± 2.8 (18–29)	22.4 ± 2.8 (18–29)	59.8 ± 5.9 (50–71)[a]	59.8 ± 5.9 (50–71)[a]
Height (cm)	161.7 ± 5.6	161.7 ± 5.6	156.8 ± 3.8[a]	156.8 ± 3.8[a]
SBP (mm Hg)	116.5 ± 10.1	116.2 ± 7.6	133.5 ± 11.8[a]	126.4 ± 8.9[c]
DBP (mm Hg)	73.6 ± 8.0	73.6 ± 6.0	82.8 ± 9.2[a]	79.3 ± 5.0[c]
Body weight (kg)	55.8 ± 6.3	55.1 ± 5.1	61.7 ± 6.2[a]	59.3 ± 6.0[c]
BMI (kg/m^2)	21.4 ± 2.9	21.2 ± 2.5	25.1 ± 2.9[a]	24.2 ± 2.7[c]
WC (cm)	68.4 ± 5.3	67.9 ± 5.0	75.8 ± 7.7[a]	74.6 ± 7.3[c]
FPG (mg/dl)	85.0 ± 10.3	81.7 ± 6.9[c]	88.8 ± 9.6	83.0 ± 6.7[c]
PG 30 min after OGTT	159.2 ± 19.1	146.1 ± 23.2[b]	171.4 ± 24.7	155.8 ± 25.6[c]
PG 60 min after OGTT	144.2 ± 21.0	138.4 ± 26.6	154.5 ± 28.8	141.5 ± 25.2[b]
PG 90 min after OGTT	129.4 ± 18.4	120.5 ± 21.2[b]	129.9 ± 27.9	120.6 ± 20.3
PG 120 min after OGTT	113.0 ± 16.3	106.3 ± 19.3	114.4 ± 22.0	104.3 ± 20.1[b]
$AUC_{glucose}$	265.9 ± 23.9	249.5 ± 33.6[b]	278.7 ± 38.3	255.8 ± 34.0[c]
FPI (μIU/ml)	10.4 ± 3.7	8.8 ± 3.4[c]	13.7 ± 3.5[a]	9.9 ± 3.1[c]
TC (mg/dl)	183.1 ± 26.0	173.1 ± 20.7[b]	207.1 ± 35.0[a]	190.1 ± 27.9[c]
TG (mg/dl)	86.4 ± 25.9	82.3 ± 18.3	125.3 ± 48.4[a]	113.9 ± 38.9[c]
HDL-C (mg/dl)	67.0 ± 11.1	70.0 ± 11.3[c]	59.1 ± 13.8[a]	66.2 ± 11.4[c]
LDL-C (mg/dl)	94.5 ± 17.9	87.9 ± 20.3[b]	116.9 ± 29.6[a]	102.7 ± 30.3[c]
HOMA-IR	2.1 ± 0.8	1.8 ± 0.7[b]	3.0 ± 0.9[a]	2.0 ± 0.6[c]
HOMA-β	242.2 ± 205.9	215.2 ± 185.6	220.4 ± 98.1	211.0 ± 132.7
$AUC_{glucose}$	265.9 ± 23.9	249.5 ± 33.6[b]	278.7 ± 38.3	255.8 ± 34.0[c]
VO_2max (ml/min)	1812.7 ± 377.4	1865.0 ± 329.9[b]	1427.9 ± 320.4[a]	1643.2 ± 324.1[b]
Adiponectin (μg/ml)	8.1 ± 2.9	10.1 ± 4.6[b]	11.8 ± 5.4[a]	16.2 ± 6.0[c]
RBP4 (μg/ml)	40.7 ± 12.2	37.7 ± 9.6	48.1 ± 15.3[a]	38.0 ± 9.3[c]

All data are expressed as the mean ± SD. Student's *t* test was used to compare means of parameters between the young and middle-aged groups, and paired *t* tests were used to analyze changes in parameters before and after exercise. C, Cholesterol; DBP, diastolic blood pressure; PG, plasma glucose; SBP, systolic blood pressure; TC, total cholesterol; TG, total glucose.

[a] $P < 0.05$ (Student's *t* test).

[b] $P < 0.05$ (paired *t* tests).

[c] $P < 0.01$ (paired *t* tests).

creased in RBP4 responders than nonresponders. After exercise, adiponectin concentrations increased by 56.6% in the younger adiponectin responder group and by 73.0% in the older responder group. Likewise, RBP4 levels were decreased by 11.4% in the younger RBP4 responders and by 28.6% in the older responders (Fig. 1). TTR levels were also decreased significantly in RBP4 responders of both age groups (Fig. 2). This was in accord with the pattern of RBP4 levels. Furthermore, there was significant correlation between changes of RBP4 and those of TTR in RBP4 responders but not in nonresponders.

Correlations between the changes in adiponectin, RBP4, and RBP4/adiponectin and the changes in various parameters

Changes in serum adiponectin levels were correlated with changes in FPI, HOMA-IR, and VO_2max in both groups. In the older group, it was also correlated with the changes in FPG and obesity indices, such as body weight, BMI, and WC. Changes of RBP4 levels were correlated with the changes of surrogate markers of insulin resistance, WC, triglycerides, and HOMA-IR in both age groups. Interestingly, the altered RBP4 level showed significant negative correlation with the change of adiponectin levels and VO_2max only in the older group ($r = -0.517$ and -0.547, $P < 0.01$). When the change (Δ) in RBP4/adiponectin was evaluated, the absolute value of the correlation coefficient showed an increase in the correlation with the relevant parameters in both groups.

Comparison between responders and nonresponders

When dividing subjects into responders and nonresponders according Δadiponectin or ΔRBP4 levels after exercise, Δadiponectin was negatively correlated with ΔFPI, ΔHOMA-IR, and $\Delta AUC_{glucose}$ and positively with ΔVO_2max only in older adiponectin responders. For the response of RBP4 to exercise, there was a positive correlation between ΔWC and ΔRBP4 in both age responder groups. Furthermore, Δtriglyceride, ΔHOMA-IR, and $\Delta AUC_{glucose}$ were positively correlated with ΔRBP4 only in older RBP4 responders. There was borderline significance in the correlations between ΔRBP4 and ΔFPG or ΔFPI.

Regression analysis for independent association with adiponectin or RBP4

To find independent association with Δadiponectin or ΔRBP4, we conducted a regression model for Δadiponectin as an independent variable including age, ΔBMI, ΔVO_2max, ΔRBP4, and ΔHOMA-IR as covariates. Finally, ΔVO_2max and ΔHOMA-IR were significantly associated with Δadiponectin after adjustment for other variables ($P = 0.009$ and $P = 0.043$, respectively). Similarly, ΔHOMA-IR was significantly associ-

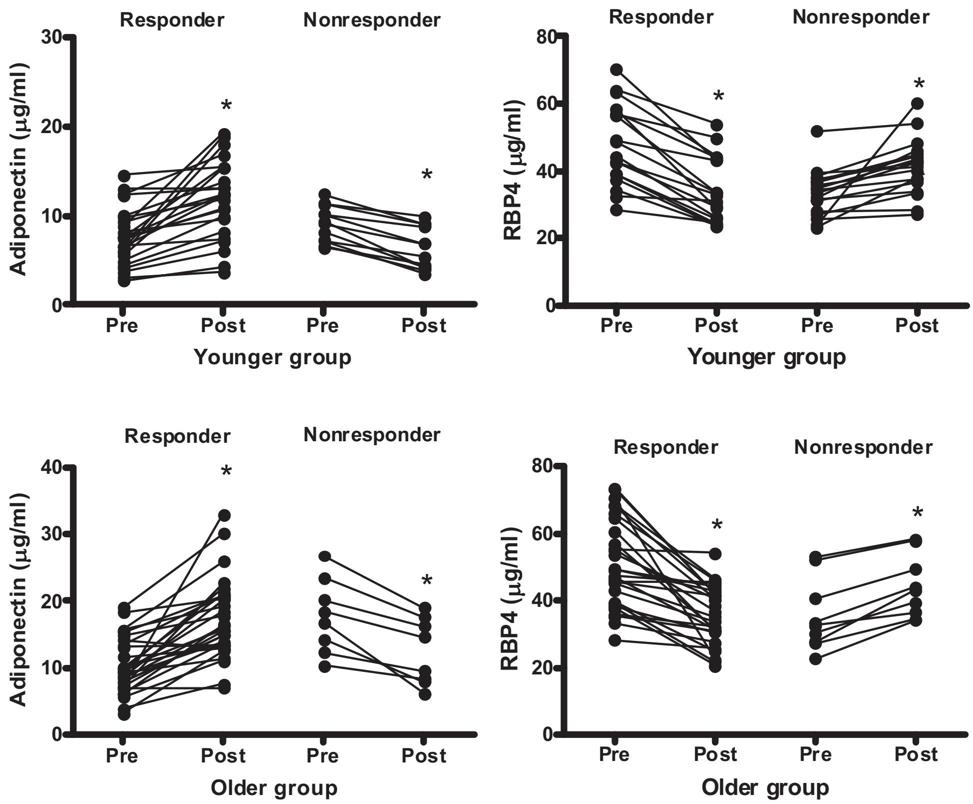

FIG. 1. Changing patterns of adiponectin and RBP4 concentrations after 10 wk of aerobic exercise program in younger and older groups of women; adiponectin concentrations were increased in 24 of 36 younger and 29 of 38 older subjects (adiponectin responders), and RBP4 levels were decreased in 18 of 36 younger and 29 of 38 older participants (RBP4 responders). *, $P < 0.05$.

ated with ΔRBP4 after adjustment for age, ΔBMI, ΔVO_2max, Δadiponectin, and ΔHOMA-IR ($P = 0.002$).

Discussion

In this study, we found that both adiponectin levels and VO_2max were significantly increased after a 10-wk supervised exercise program in groups of both younger and older women. Interestingly, the serum levels of RBP4 were decreased only in the older group. Furthermore, exercise-induced changes of adiponectin or RBP4 levels were significantly correlated with changed insulin resistance parameters and obesity indices in both age groups. These suggest that insulin-sensitizing effects of exercise are associated with decreased RBP4 and increased adiponectin in both young and old women.

Aerobic conditioning, assessed by VO_2max during exercise, increased only marginally in the younger group who had relatively higher VO_2max levels and low insulin concentration and showed slightly improved insulin sensitivity. However, in the older group with higher insulin concentration and HOMA-IR, exercise training increased VO_2max more than in the younger group and was associated with reductions in BMI, WC, and fasting insulin level and an increase in HDL-cholesterol. Additionally, in a large cohort study, stronger inverse associations were observed between physical activity and coronary heart disease risk among women who were overweight or had elevated cholesterol levels than those that did not (23). It thus appears that insulin-sensitizing effects of exercise are more effective in older women, who are relatively more insulin resistant and obese than younger women.

The degree of changes in circulating adiponectin and RBP4 levels after exercise was much greater in the older than younger group. It is conceivable that the basal RBP4 level in old women but not in young women may be sufficient to be altered by 10 wk of exercise training. This is further supported by the recent findings that the effects of exercise were clearer in those with high initial RBP4 levels (12). Along with this, we also found that there was a higher correlation between the changes in RBP4 concentration and VO_2max in the older group, which could be explained by differences in basal RBP4 levels between the two groups. Thus, the effect of exercise and its relationship with insulin resistance seem to be more evident in older subjects who are less fit and relatively insulin resistant.

Interestingly, there were discrepancies in the effects of exercise on adiponectin and RBP4 levels between responders and nonresponders in this study, which are defined by their individual response of adiponectin or RBP4 by exercise.

One possible explanation for this is that the insulin-sensitizing effect of exercise could be different for each individual. Recent studies demonstrated that the response of RBP4 to 1 month of exercise training was variable (12), and RBP4 levels were decreased after exercise mainly in the subjects having higher RBP4 levels at baseline. Similarly, the older group in our study, who had higher RBP4 level at baseline, showed a greater decrease in RBP4 level. However, we can exclude the possibility of dif-

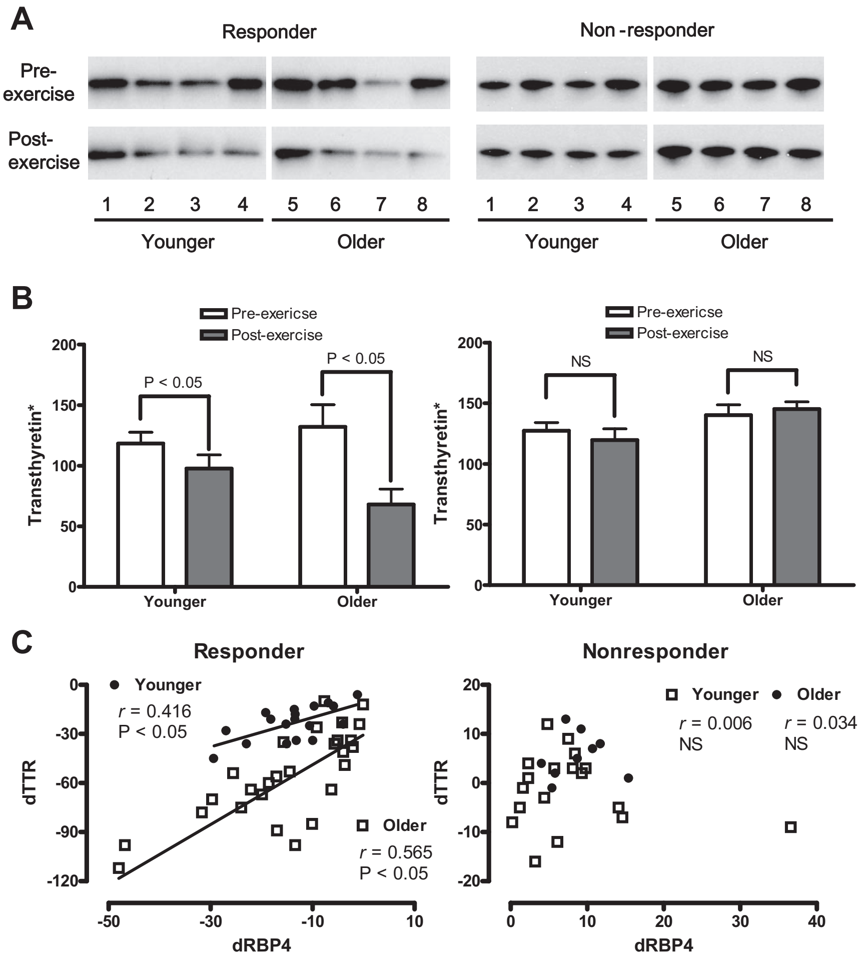

FIG. 2. Changes of TTR levels in RBP4 responders and nonresponders of both age groups after exercise program. A, Western blotting of TTR; B, changes of mean TTR levels in both age groups (*, arbitrary units); C, correlation between changes of RBP4 and TTR by their response. NS, Not significant.

fering degrees of exercise because we supervised the intensity and time of exercise of each individual at every visit. Mean ± SD of percent maximal heart rate during the exercise session was also almost the same between two groups: 74.6 ± 12.1% in the younger group and 73.4 ± 8.7% in the older group ($P > 0.05$).

Similarly, the adiponectin levels were elevated in response to 10 wk of exercise training in both young and old women but not all. This also can be explained by the fact that insulin-sensitizing effects of exercise on adiponectin could be different for each individual.

Consistent with a previous report (6), we found that TTR levels were higher in older women than in younger women. TTR levels were decreased in response to 10 wk of exercise training in the RBP4 responders, but there was no significant change in the nonresponders. Importantly, the changes of RBP4 level were significantly correlated with those of TTR in RBP4 responders but not in nonresponders. In serum, RBP4 is bound almost entirely to TTR in a 1:1 molar complex (7). Binding of RBP4 to the TTR tetramer (56 kDa) is known to stabilize RBP4 in the circulation by prohibiting renal excretion (7, 8). Thus, our results could be explained by the fact that degree of glomerular filtration of RBP4-TTR complex may be different or that RBP4-TTR affinity is different between responders and nonresponders.

Of note, the younger group had lower adiponectin levels despite being more insulin sensitive and having lower BMI in this study. Relatively little is known regarding the circulating adiponectin levels between different-aged groups in nondiabetic subjects. A recent study with nondiabetic women showed adiponectin values were higher in older compared with younger women (24). Similarly, higher adiponectin levels were observed in older postmenopausal women compared with young premenopausal women (25). Taken together, age, body composition, and menopausal status may be important factors in regulating adiponectin concentration in healthy women.

In conclusion, a 10-wk, moderate-intensity, regular exercise program improved VO_2max and insulin resistance parameters and modified adiponectin and RBP4 concentrations, particularly in older women, who were more relatively insulin resistant. These data suggest that exercise, having an insulin-sensitizing effect, could be a good therapy to prevent or delay diabetes and cardiovascular diseases in middle-aged women through the modification of adiponectin or RBP4 levels.

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