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Research article

Circuit resistance exercise improves glycemic control and adipokines in females with type 2 diabetes mellitus

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Abstract

The aim of study was to evaluate whether circuit resistance exercise (CE) improves glycemic control and adipokine levels in comparison with walking exercise (WE) in 15 adult postmenopausal Korean females with type 2 diabetes mellitus (T2DM). The participants were randomly assigned to either the CE or WE group. Subjects exercised for 1 h, three times per week for 12 weeks. The parameters measured were body composition, respiratory rate, blood glucose, insulin and adipokines. The body composition of the CE group showed a significant reduction (all $p < 0.05$) in body weight, body mass index (BMI), and percentage of body fat and a significant increase in muscle mass. Respiratory function was also significantly increased in the CE group. Additionally, hemoglobin A1c (HbA1c) changed favorably in the CE group, as were the concentrations of adipokines such as retinol binding protein 4 (RBP-4) ($p < 0.05$), adiponectin ($p < 0.01$), and monocyte chemoattractant protein-1 (MCP-1) ($p < 0.01$). In addition, significant correlations with CE were evident for homeostatic model assessment insulin resistance (HOMA-IR) and glucose ($r = 0.69$, $p < 0.001$), muscle mass and glucose ($r = 0.45$, $p < 0.05$), and muscle mass and HbA1c ($r = 0.39$, $p < 0.05$). The beneficial effects of CE include the development of muscle mass, which effectively increases glucose use and reduces the amount of insulin required. Thus, our results suggest that CE improves glycemic control and adipokines resulting from incrementally increased muscle mass and reductions of body weight, BMI and percentage of body fat for T2DM postmenopausal Korean women.

Key words: Circuit resistance exercise, walking exercise, glycemic control, adipokines, type 2 diabetes mellitus.

Introduction

Exercise plays an important role in the management of type 2 diabetes mellitus (T2DM). Traditionally, aerobic and endurance exercise have been recommended for older patients with T2DM and have been associated with weight loss, improved glucose tolerance, and increased cardiovascular fitness (Agurs-Collins et al., 1997; Ligtenberg et al., 1997; Tessier et al., 2000). In addition, the American Diabetes Association and American College of Sports Medicine recommend the use of resistance training as part of a well-rounded exercise program for older individuals (ACSM, 2000; Albright et al., 2000).

Given that the prevalence of T2DM increases with age (Dunstan et al., 2002) and that aging is associated with reduced muscle strength and metabolic control both of which are influenced by progressive age-related decline in muscle mass (Evans, 1995), resistance training may represent an effective exercise alternative for older adults. Furthermore, several studies in older non-diabetic patients have demonstrated that resistance training can improve muscular strength and may be an effective tool for the prevention of age-related sarcopenia (Brown et al., 1990; Frontera et al., 1988; Pyka et al., 1994).

In general, excess adipose tissue or obesity, particularly in the visceral compartment, is associated with insulin resistance, hyperglycemia, dyslipidemia, hypertension, and prothrombotic and proinflammatory states (Grundy et al., 2004). Also, it was suggested that the endocrine functions of adipose tissue may be amplified by the adverse metabolic consequences of both adipose tissue excess and deficiency (Grundy et al., 2004).

Although various adipose tissue-derived hormones have been identified, even well-characterized factors such as leptin require further evaluation to more precisely define their physiological roles. In addition to known genes, as many as 40% of genes expressed in adipose tissue are novel, and 20-30% of these may be secreted proteins (Maeda et al., 1996). An adipokine or adipocytokine secreted by adipose tissue induces insulin resistance in the liver and skeletal muscle (Abel et al., 2001). Retinol binding protein 4 (RBP4) has been identified as such a factor (Yang et al., 2005). Recently, the mechanism by which RBP4 impairs insulin signaling in skeletal muscle and affects glucose output in the liver was explored (Tamori et al., 2006).

Most studies on the effects of exercise on circulating adipokine levels have reported inconsistent findings (Gutin et al., 1999; Hulver et al., 2002; Kriketos et al., 2004; Pasman et al., 1998; Ryan et al., 2003; Yatagi et al., 2003; Yokoyama et al., 2004; Hara et al., 2005). Nevertheless, exercise is important in those with T2DM because it can improve glucose uptake by lowering both insulin resistance and body fat. In particular, the specific effects of circuit resistance exercise (CE) on adipokine levels have not been clearly demonstrated in people with T2DM. Therefore, the present study was initiated to prospectively evaluate the changes in glycemic indices and circulating concentrations of adipokines in postmenopausal women with T2DM who participated in a 12 week, three times per week exercise training programs involving either CE or walking exercise (WE).

Methods

Patients

Seventeen T2DM, postmenopausal women registered at

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Dong-A University Hospital (DAUH) participated in this study. Their mean age was 51.10 ± 1.10 years and mean BMI was 23.38 ± 3.42 $kg \cdot m^{-2}$ Two subjects were eliminated for not adhering to protocol; the remaining 15 volunteers completed the study protocol. All subjects provided written informed consent to take part in this study. Subjects were randomly assigned to either the WE group (n = 7) or the CE group (n = 8). The researchers were blind to metabolic parameters. Participants were selected based on a lack of complex disease, HbA1c level of 7~10%, and fasting blood glucose of at least <200$mg \cdot dl^{-1}$. Also, no subjects received insulin therapy, and no medications were altered during the exercise treatment. Before inclusion in the study, all candidates underwent an extensive medical history screening. The experimental protocol was approved by the Institutional Review Board (IRB) of DAUH.

Measurement of body composition and VO_2max

Before beginning the exercise program, all subjects underwent anthropometric measurements (body weight, BMI, percentage of fat and muscle mass). Body composition was measured by the bioelectrical impedance method (VENUS 5.5 in Korea).All subjects performed maximal exercise determined by the modified Bruce protocol. Participants underwent a treadmill (Taeha, Korea) exercise test and maximal oxygen uptake (VO_2max $ml \cdot kg^{-1} \cdot min^{-1}$) was determined using a Quark b2 analyzer (Cosmed, Rome, Italy) after a 3 minute rest. Perceived exertion was rated every minute using the Borg scale. Attainment of VO_2max was validated if two of the following four established criteria (ACSM, 2000) were satisfied: oxygen uptake plateau despite increasing exercise intensity (≤120$ml \cdot min^{-1}$), respiratory exchange ratio ≥ 1.15, maximal heart rate within 10 $beats \cdot min^{-1}$ of the age-predicted maximal value, and a Borg scale value ≥ 17.

Blood sampling and analyses

Blood samples were drawn from the median cubital vein after an 8 h overnight fast. Each blood sample was divided in individual tubes and centrifuged at 3,000 rpm for 10 min at 4°C. All samples were immediately frozen and submitted for measurement of adiponectin, RBP4, monocyte chemoattractant protein 1 (MCP-1), and C-reactive protein (CRP). The serum adiponectin and RBP4 were quantified by an enzyme-linked immunosorbent assay (AdipoGen, Seoul, Korea) using a standard curve constructed with a dilution series of a provided human RBP4 sample (R^2 = 0.99 for standard-curve linear regression) and adiponectin (R^2 = 0.93 for standard-curve linear regression). The inter-assay coefficient of variation as measured by a control provided by the manufacturer with each plate was 10.2% for RBP4 and 2.8% for adiponectin. The intra-assay coefficient of variation (measurement of six identical serum samples on each plate) was 9.2% for RBP4 and 2.9% for adiponectin. Also, adiponectin and RBP4 were quantified using a polyclonal antibody recognizing native human adiponectin and RBP4 and a series of plates having wells coated with predetermined amounts of recombinant human adiponectin and RBP4. Their relative reactivity was plotted with those of the standard proteins. HbA1c levels were determined by high-performance liquid chromatography using commercially available kit reagents (VARIANT II HbA1c Reorder Pack; Bio-Rad, Hercules, CA, USA). Insulin resistance in the fasting state was determined by the homeostasis model assessment (HOMA-IR) using the formula: [fasting plasma glucose ($mg \cdot dl^{-1}$) fasting plasma insulin ($\mu U \cdot dl^{-1}$)] ÷ 405

Exercise program

Both groups of subjects performed the same quantity of exercise: approximately 1 h 3 times per week for 12 weeks. WE group participants (mean age; 52.5 ± 2.15 years, mean height; 1.57 ± 0.02 m) began exercising at 60% of heart rate reserve (HRR) by walking along a track. During each session, the CE participants (mean age; 50.4±2.14 years, mean height; 1.56 ± 0.02 m) performed stair climbing, stationary cycling, and resistance exercises (lat pull-downs, abdominal exercises, leg curls, leg extensions, and bicep curls, 12 repetitions of each exercise per set, three set) at 60% of HRR (including a 10 min warm-up and cool-down). During the 12 week program the target calorie consumption was 4.0 $kcal \cdot kg^{-1}$. The daily exercise calorie consumption was divided into energy expenditure per minute at an HRR of 60%, and exercise hours were calculated.

Statistical analyses

All values of body composition, adipokine and T2DM risk factors are expressed as mean±SE. All the data were tested for their normal distribution using Shapiro-Wilk test. The effects of exercise on each variable were evaluated by paired t-test and independent t-test. Correlation analysis was performed by using Spearman's test. All statistical analyses were performed using SPSS version 14.0 (SPSS, Chicago, IL, USA). Statistical significance was accepted at an α value of 0.05.

Results

The characteristics of CE and WE group at the beginning of the study are shown in Table 1. After the 12 week exercise program, CE participants displayed a significant reduction in body weight, BMI, and percentage body fat and a significant increase in muscle mass. In addition, body weight and percentage of body fat were significantly different between the exercise groups ($p < 0.05$). Table 2 shows VO_2rest and VO_2max results obtained during the treadmill test. There were no differences in the rest test values in either group. However, VO_2max and VE were significantly increased ($p < 0.05$) after the maximal test in the CE group after 12 weeks, and VE was also changed significantly between groups ($p < 0.05$). T2DM risk factors changed significantly between participants in the CE and WE groups (Table 3). In the CE group, HbA1c decreased significantly ($p < 0.01$) at baseline rest (BR) as comparison to the exercise training rest (TR) after 12 weeks. Also, both groups displayed significant decreases in baseline max (BM) compared to the 12 weeks exercise training max (TM) ($p < 0.05$ for CE or WE, $p < 0.01$ for WE or CE). In WE participants, insulin decreased significantly at BR compared to TR ($p < 0.05$) and at TR compared to TM ($p < 0.05$). In addition, C-peptide

Table 1. Changes in body composition after 12 weeks exercise training. Data are means (±SE).

Variable		Baseline	12 weeks
Weight (kg)	**CE**	53.3 (1.6)	51.9 (1.7) †
	WE	57.9 (2.9)	56.3 (2.8) *
BMI (kg·m^{-2})	**CE**	22.0 (.8)	20.9 (.8) †
	WE	23.6 (1.4)	23.0 (1.3)
Percent body fat (%)	**CE**	29.4 (.8)	27.3 (1.2) †
	WE	31.1 (1.9)	30.1 (1.8) *
Muscle mass (kg)	**CE**	23.9 (1.1)	25.7 (.8)
	WE	26.1 (1.0)	26.7 (1.0)

† $p < 0.05$ baseline rest (BR) vs. 12 weeks rest (TR), * $p < 0.05$ between groups.

decreased in BR compared to TR ($p < 0.05$) and at BM compared to TM ($p < 0.01$) significantly. In the CE group, significant increases in glucose were evident at BR compared to BM ($p < 0.05$) and at TR comparison to TM ($p < 0.05$) significantly. C-peptide at TM changed significantly between the CE and WE groups ($p < 0.05$).

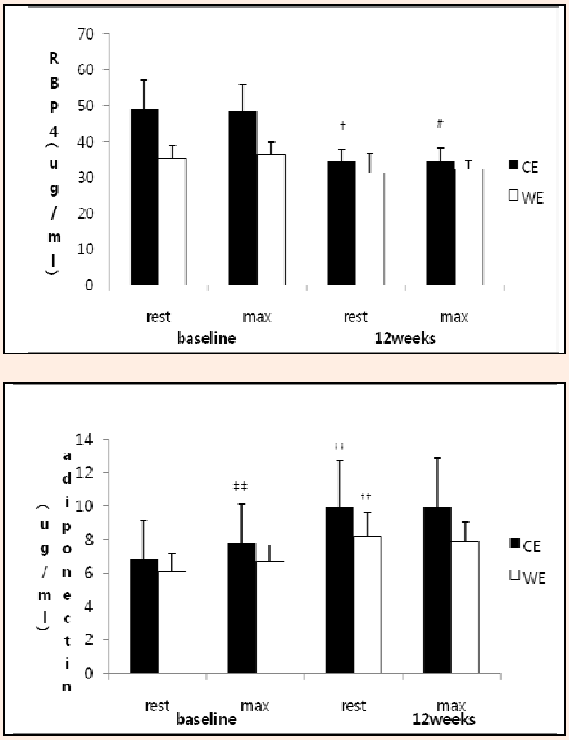

Figure 1. Changes in adipokines after 12 weeks of exercise training.

Figure 1 shows the changes of adipokine levels during the 12 week period in both exercise group. In the CE group, RBP-4 decreased significantly at BR compared to TR (both $p < 0.05$) and at BM compared to TM ($p < 0.05$). In the CE group, adiponectin increased significantly at BR compared to TR and BR compared to BM (both $p < 0.01$). Adiponectin levels in the WE group also increased significantly at BR compared to TR ($p < 0.01$). Figure 2 shows the changes of cytokine levels during of 12 weeks both exercise program. In the CE group, MCP-1 increased significantly at BR compared to TR ($p < 0.01$), at BR compared to BM ($p < 0.01$), at BM compared to TM ($p < 0.01$), and at TR compared to TM (all $p < 0.01$). WE participants also displayed significant increases at BR compared to TR ($p < 0.01$) and at BM compared to TM ($p < 0.05$). The TM MCP-1 value was changed significantly between the WE and CE groups ($p < 0.01$). Figure 3 depicts the correlation coefficients of HOMA-IR and glucose ($r = 0.69$, $p < 0.001$), muscle mass and glucose ($r = 0.45$, $p < 0.05$), and muscle mass and HbA1c ($r = 0.39$, $p < 0.05$), respectively.

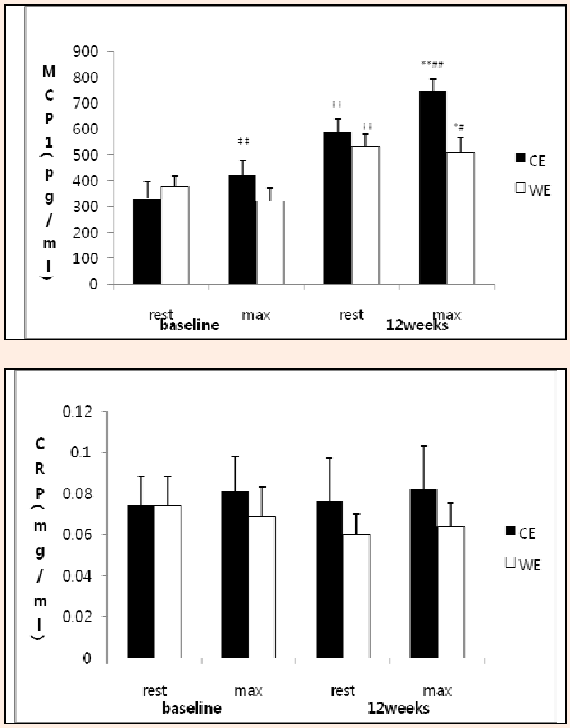

Figure 2. Change in cytokines 12 weeks of exercise training.

Discussion

In this study, we investigated whether CE improves glycemic control and adipokine levels in comparison with WE in adults postmenopausal females with T2DM. The results clearly show that the CE programs improved effective body composition, glycemic control and adipokine levels, in comparison to WE. In particular, significant improvements were evident after 12 weeks in weight, BMI, percent body fat, muscle mass, VO_2max, HbA1c and RBP4 of CE participants. The results provided further evidence that CE decreases insulin resistance and improves adipokine levels resulting from increased muscle mass and decreased body fat.

Individual exercise sessions varied from at least 30 min for resistance training (Dela 2004; Loimaala 2003) to

Table 2. Changes in VO_2rest and VO_2max after 12 weeks of exercise training. Data are means (±SE).

		Baseline		12 weeks	
Variable	**Group**	**Rest**	**Max**	**Rest**	**Max**
VO_2 (ml·kg^{-1}·min^{-1})	**CE**	4.26 (.34)	29.53 (1.17)	4.34 (.35)	32.08 (1.41) #
	WE	3.72 (.32)	26.16 (1.15)	3.63 (.48)	27.40 (1.39) *
HR (beat·min^{-1})	**CE**	81 (2)	166 (4)	80 (2)	168 (4)
	WE	81 (3)	163 (5)	78 (4)	164 (4)
VE (l·min^{-1})	**CE**	9.42 (.69)	54.37 (3.50)	9.69 (.76)	58.35 (3.58) #
	WE	8.89 (1.11)	50.24 (4.15)	7.69 (.78)	51.56 (3.40) *

# $p < 0.05$ baseline max (BM) vs 12weeks max (TM), * $p < 0.05$ between groups.

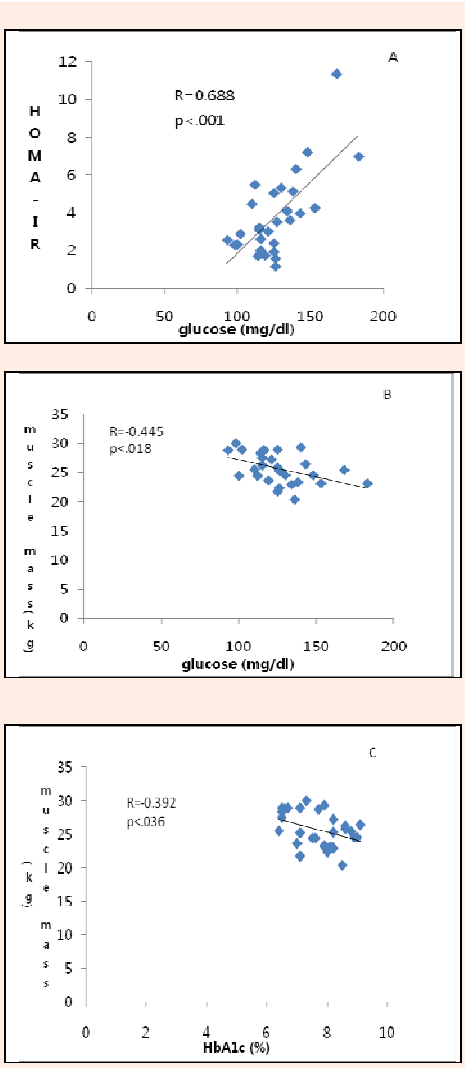

Figure 3. Correlation of HOMA-IR and glucose (p<.001), muscle mass and glucose (p < 0.05), and muscle mass and HbA1c (p < 0.05).

120 min for a Qi Gong program (Tsujiuchi 2002). Other studies using Qi Gong involved a 2 h weekly session and required participants to complete one unsupervised session in addition to the three (Loimaala 2003; Wing 1988) or two (Raz 1994) sessions supervised by researchers. Aerobic exercise is less effective than resistance exercise at lowering weight and percentage of body fat, while resistance exercise effectively increases muscle mass.

High intensity resistance training in T2DM individuals results in decreased weight and body fat and increased lean body mass (Dunstan et al., 2002). In another study, a 16 week structured aerobic and resistance training program consisting of three sessions per week achieved significantly decreased body weight in T2DM participants as compared with aerobic training alone(Cuff et al., 2003). While aerobic exercise lowers body weight, resistance exercise may increase insulin sensitivity by increasing muscle mass (Janssen et al., 2002). A high intensity progressive resistance training program involving nine upper and lower body exercises performed 3days each week led to a significant reduction in HbA1c after 3months, which was decreased further after 6months of training (Dunstan et al., 2002). Finally, a meta-analysis of 15 papers suggested that regular exercise in those with T2DM lowers weight and improves HbA1c values (Boule et al., 2001).

It has been well-established that plasma concentrations of anti-inflammatory cytokine such as interleukin-4 and -10 and MCP-1 are increased after maximal exercise (Brenner et al., 1999; Peake et al., 2005; Suzuki et al., 2003). Increased production of anti-inflammatory cytokines during exercise may result in enhanced susceptibility to infections via alterations in the pro- versus anti-inflammatory cytokine balance toward a stronger anti-inflammatory response (Suzuki et al., 2003). The present study revealed that plasma MCP-1 levels of both groups significantly increased in maximal exercise testing after 12 weeks exercise training with the plasma MCP-1 levels of the CE participants being significantly increased in each maximal exercise test before and after the 12 weeks period. These results are consistent with the view that exercise training induces a greater increase of anti-inflammatory compounds than of pro-inflammatory compounds. Furthermore, the study indicates that the circuit resistance exercise training may contribute to a greater beneficial effect in plasma MCP-1 levels than walking exercise training.

The view that adipose tissue and adipocytes act simply a storage depot for fat is no longer tenable. Adipokines such as adiponectin and RBP4 appear to be a major modulator of insulin action and their levels are reduced and increased, respectively, in T2DM, which could contribute to peripheral insulin resistance in this condition (Chandran et al., 2003). Some studies (Hulver et al., 2002; Reaven 2005; Yatagi et al., 2003) have reported that adiponectin concentrations remain unchanged in subjects after long-term exercise. Recently, however, Hara et al., (2005) reported that a combination of stationary cycle exercise (3 days·week^{-1}, 60 min each time) and resistance training (same frequency and duration) improves body composition and adiponectin levels.

Table 3. Change in risk factors of type 2 diabetes mellitus after 12 weeks of exercise training. Data are means (±SE).

		Baseline		12 weeks	
Variable	**Group**	**Rest**	**Max**	**Rest**	**Max**
HbA1c (%)	**CE**	8.01 (.35)	8.07 (.36)	7.36 (.28) ††	7.37 (.30) ##
	WE	8.21 (.41)	8.37 (.43)	8.00 (.38)	7.91 (.40) #
Insulin (μU·dl^{-1})	**CE**	13.45 (2.53)	12.29 (1.72)	11.41 (1.87)	10.17 (1.02)
	WE	17.04 (4.76)	14.57 (3.24)	10.64 (1.49) †	8.29 (1.10) *
C-peptide (ng·dl^{-1})	**CE**	2.83 (.75)	2.63 (.74)	1.99 (.37)	1.84 (.34)
	WE	2.46 (.66)	2.46 (.62)	1.22 (.15) †	.87 (.17) # ψ
Glucose (mg·dl^{-1})	**CE**	136.4 (8.8)	139.1 (8.0) ‡	129.3 (10.6)	140.0 (10.1) *
	WE	121.3 (10.0)	126.4 (10.3)	119.8 (8.3)	113.9 (8.4)
HOMA-IR	**CE**	4.57 (.92)	4.19 (.58)	3.70 (.77)	3.49 (.39)
	WE	4.96 (1.26)	4.46 (.87)	3.26 (.57)	2.39 (.43) #

† and †† denote $p < 0.05$ and 0.01 respectively, baseline rest (BR) vs. 12 weeks rest (TR), ‡ $p < 0.05$ baseline rest (BR) vs. baseline max (BM), * $p < 0.05$ 12 weeks rest (TR) vs. 12 weeks max (TM), # and ## denote $p < 0.05$ and 0.01 respectively, baseline max (BM) vs. 12 weeks max (TM),ψ $p < 0.05$ between groups.

Yokoyama et al., (2004) suggested that stationary cycle exercise performed for 40 min·day^{-1}, 5 days·week^{-1} at a mean intensity of 50.6%~58.6%, improves adiponectin levels. Kriketos et al., (2004) also reported that aerobic exercise (4-5 days·week^{-1} for 40 min per session, at 55%~70% of VO_2max, for 10 weeks) substantially increases (260%) adiponectin levels. The present results suggests that CE induced weight loss and muscle mass incrementally increases the level of adiponectin secreted by adipocytes, due to heightened glucose utilization. Such aerobic exercise has been shown to decrease body weight, fat and adipokines in high intensity and frequency, while resistance exercise decreases these in low intensity, time and frequency.

Increased blood levels of RBP4 correlated with obesity, insulin resistance, impaired glucose tolerance, and T2DM (Graham et al., 2006). Elevation of serum RBP4 in insulin-resistant states may be a consequence of increased gene expression, expanded fat mass, altered secretion, and clearance from the circulation (Yang et al., 2005). Plasma RBP4 concentrations are elevated in subjects with impaired glucose tolerance or T2DM and may be related to various clinical parameters known to be associated with insulin resistance (Cho et al., 2006).

Increased serum RBP4 correlates with insulin resistance in humans with impaired glucose tolerance or T2DM as well as in non-obese, non-diabetic subjects with strong family histories of type 2 diabetes (Graham et al., 2006). In non-obese subjects, decreased expression of GLUT4 in adipocytes is correlated with both increased serum RBP4 levels and insulin resistance. Although the mechanisms responsible for this correlation are unknown, it may involve glucose sensing by adipocytes (Tamori et al., 2006). Unclearly, the present study is unexpected the relationship between inflammatory factors and serum RBP4 because serum RBP4 is found to be reduced in many clinical setting associated with inflammation (Baeten et al., 2004; Rosales et al., 1996). However, presently, exercise training by T2DM postmenopausal females led to a reduction in RBP4 levels because of reduced weight and percentage of body fat, and serum RBP4 levels were inversely correlated with the level of adiponectin in adipocytes. RBP4 concentrations have been shown to be related to insulin resistance both in cross-sectional and longitudinal analyses (Graham et al., 2006; Tamori et al., 2006; Yang et al., 2005). Our findings support a functional relevant relationship between RBP4 and insulin resistance in type 2 diabetic patients. Consistent with this, exercise improves circulating adipokine levels in obese individuals (Kondo et al., 2006) and those with type 2 diabetes (Graham et al., 2006).

Conclusion

Our study demonstrates that CE may result in significantly improved levels of body composition, glycemic control and adipokines. The study also indicates that the beneficial effects of CE include the development of muscle mass and reduced percentage of body fat, which effectively increases glucose use and reduces the amount of insulin required. We conclude that CE improves glycemic control and adipokines resulting from incrementally increased muscle mass and reduction of body weight, BMI and percentage of body fat in T2DM postmenopausal Korean women.

Acknowledgments

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Key points

- CE-induced weight loss and muscle mass increment increases the level of adiponectin secreted by adipocytes due to heightened glucose utilization and fat oxidation.
- Aerobic exercise decreases body weight, fat and adipokines in high intensity and frequency, while resistance exercise decreases these parameters in low intensity, time and frequency.
- CE can improves glycemic control and adipokines resulting from reduction of body fat postmenopausal Korean women with T2DM.

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