Interactive Effect of an Acute Bout of Resistance Exercise and Dehydroepiandrosterone Administration on Glucose Tolerance and Serum Lipids in Middle-Aged Women

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Abstract

The present study determined the interactive effect of an acute bout of resistance exercise and dehydroepiandrosterone (DHEA) administration on glucose tolerance and serum lipids. Twenty middle-aged female subjects performed an acute bout of resistance exercise and were subsequently divided into two groups: placebo (age 40.7 ± 2.0) and DHEA administered (age 39.0 ± 2.7). Ten subjects who received DHEA (age 41.5 ± 4.6) participated in a non-exercise control. DHEA (25 mg twice daily) or placebo was orally supplemented for 48 hours. Before exercise and 48 hours after the last exercise bout (14 hours after the last DHEA intake), an oral glucose tolerance test and an insulin concentration were determined. Levels of fasting serum cholesterol and triglyceride, tumor necrosis factor-α (TNF-α), creatine kinase (CK) were also measured. The DHEA administration significantly elevated the fasting dehydroepiandrosterone sulfate (DHEA-S) level by approximately 3-fold. Both acute resistance exercise and DHEA administration improved glucose tolerance, but no addictive effect was found. Furthermore, exercise and DHEA administration did not affect serum triglyceride and cholesterol levels, but both lipids were significantly lowered when DHEA was given following exercise. Resistance exercise induced elevations in serum CK and TNFα levels, but these increases were attenuated by the DHEA administration. The new finding of this study was that post-exercise DHEA administration decreased serum triglycerides and cholesterol. This effect appeared to be associated with its TNF-α lowering action.

Key Words: insulin resistance, diabetes, cholesterol, DHEA, aging

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Introduction

Insulin resistance is characterized by an elevation in postprandial glucose and insulin levels. This state has been thought to associate with the development of dyslipidemia (4, 12), and considered as a common pathogenic origin of several age-associated metabolic disorders (19). A recent longitudinal study suggests that insulin sensitivity is a predictor for the incidence of type 2 diabetes, cardiovascular diseases, hypertension, stroke, and cancer in mid-aged adults (8). Therefore, a method for preserving normal insulin sensitivity might be a preventive strategy for reducing morbidity and mortality in this age group. Numerous reports have confirmed the benefit of regular exercise training on improving insulin sensitivity and glucose tolerance in human and animals with both normal and pathological conditions (13). On the other hand, the attenuations in insulin sensitivity and glucose tolerance occur progressively with an advancing age (7, 18), and the beneficial effect of exercise training for improving insulin sensitivity is also attenuated with age. Insulin sensitivity can be improved by doing exercise training in younger people, but not as effective in middle-aged or older groups (21). Therefore, combination of exercise training and anti-aging intervention might be a better method to optimize the beneficial effect of exercise on insulin sensitivity and the blood lipid profile for middle-aged people. Recent study has shown that age-associated mortality is concomitantly associated with the high insulin (an indicator of insulin resistance) and low dehydroepiandrosterone sulfate (DHEA-S) levels (14, 20). This concurrent age-dependent change led us to hypothesize that administration of this the adrenal steroid hormone with exercise might be beneficial for preventing the trend toward insulin resistance and age-associated metabolic disorders. From the outcomes of this study, we determined the interactive effect of acute resistance exercises and DHEA administration on glucose tolerance, insulin sensitivity, and serum lipid levels in normal middle-aged subjects.

Materials and Methods

Human Subjects

Twenty middle-aged pre-menopausal female subjects were double-blinded and randomly divided into two groups: placebo (age 40.7 ± 2.0, N=10) and DHEA supplemented (age 39.0 ± 2.7, N= 10). Additionally, 10 subjects who received DHEA (age 41.5 ± 4.6) participated in a non-exercise control. Aims and methods were explained to all subjects, who then signed a formal consent. This work was conducted in accordance with the guidelines in the Declaration of Helsinki. Ethical approval for the study was obtained from the Human Subject Committee of Taipei Physical Education College (TPEC).

Resistance Exercise Program

All subjects attended an acute bout of resistance training consisted of a 5-min warm-up and a 5-min cool-down period of low-intensity stationary cycling and a 60-min of resistance training (dynamic exercise involving concentric and eccentric contractions). The resistance was set at approximately 50% of each individual's 1-RM. The 1-RM was defined as the maximum amount of resistance that could be moved through the full range of motion of an exercise for no more than one repetition. Subjects followed an individually monitored progressive resistance training program by using a multiple-station weight machine. Six kinds of exercises were used for the training: bench press, leg extension, upright row, lateral pull-down, standing leg curls (ankle weights), and abdominal curls. All subjects were required to perform each repetition in a slow, controlled manner, with a rest of 2-3 min between sets. Three sets of 10 repetitions were performed for all exercises at each training session. All sessions were supervised to ensure the correct techniques and to monitor the appropriate amount of exercises and rest intervals.

DHEA Administration

Following the training section, subjects were recovered for 48 hours with supplementation of either 25 mg of dehydroepiandrosterone (DHEA) (General Nutrition Corp., Pittsburgh, PA, USA) or placebo (gelatin) twice daily until the day before an oral glucose tolerance test. Dosage of DHEA was used following that of Brown *et al*. (3), in which serum concentrations of free and total testosterone, estrone, estradiol, estriol, and lipids were not affected by the administration. They were orally given immediately after breakfast and dinner for two days. Serum DHEA-S was determined in the morning under fasted condition (before treatments and 14 hours after the last DHEA intake). An oral glucose tolerance test (OGTT) and insulin concentration were then determined on the next morning under fasted condition (8-9 am). Fasting serum cholesterol and triglyceride, CK, and TNF-α levels, were also measured.

Oral Glucose Tolerance Test (OGTT) and Insulin Response

An oral glucose tolerance test (OGTT) and insulin response during the OGTT were performed

before and 48 hours after the resistance exercise program. The test procedure was done according to the method previously described by Lee *et al*. (15). A 75-gram of glucose (Roquette Italia S.p.A., Cassano Spinola, Alessandria, Italy) was orally delivered with 500 ml of pure water. Blood samples were collected from the fingertips at 0 (fasting value), 30, 50, and 80 min. A glucose analyzer (Lifescan, CA, USA) was utilized for glucose concentration determination. Serum sample was collected from 200 µl of fingertip blood and used for insulin determination. The insulin was determined on the ELISA analyzer (Tecan Genios, Salzburg, Australia) with the use of commercially available ELISA kits (Diagnostic Systems Laboratories, Inc. Webster, TX, USA), according to the manufacture's instruction.

Serum DHEA-S and TNF-α Levels

Serum samples for measuring fasting DHEA-S and TNF-α were also drawn from finger tips, under fasting and resting conditions in the morning. These hormones were quantified on the ELISA analyzer with the use of commercially available ELISA kits (Biosource International, Nivelles, Belgium and Endogen Inc., Woburn, MA, USA).

Serum Triglyceride, Cholesterol, and Blood CK Levels

Fasted sample was used for determination of creatine kinase (CK), triglycerides and cholesterol. Total serum cholesterol and triglyceride were measured on a Beckman spectrophotometer analyzer with Sigma Trinder's reaction (Sigma, St. Louis, MO, USA), according to the manufacturer's procedure. CK was directly determined on a Reflotron Plus Analyzer according to its standard procedure provided by the manufacture (Roche Diagnostic, Basel, Switzerland).

Statistical Analysis

A one-way analysis of variance (ANOVA) with a repeated measure was used to compare the mean differences between all measured values before and after the acute resistance exercise for both DHEA and placebo subjects. Fisher's protected least significant test, which holds the value of type I error to 0.05 for each test, was used to distinguish the differences between pairs of groups. A level of $P < 0.05$ was considered significant on all tests, and all values are expressed as means ± standard errors. Power estimation was calculated to determine a sample size. A total of 24 subjects would have been required for 80% power. We initially had 30 subjects in this study and thus met the sample size necessary to detect statistical differences.

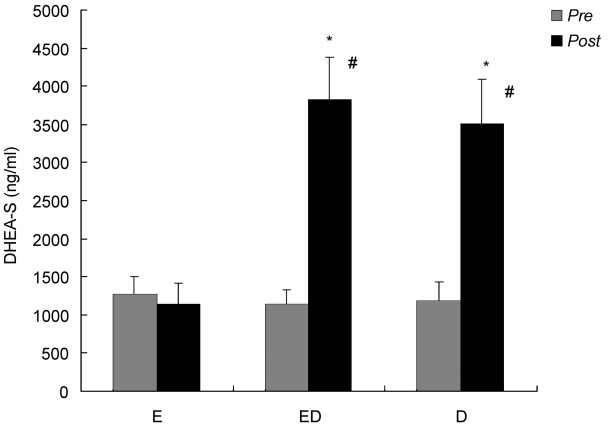

Fig. 1. Serum dehydroepiandrosterone-sulfate (DHEA-S) level after oral DHEA administration. E: resistance exercise followed by placebo supplementation. ED: resistance exercise followed by DHEA administration. D: non-exercise control with DHEA administration. *Pre*: before treatments. *Post*: 48-h after treatments. #Significant difference from the *Post* for the E group as a non-DHEA control ($P < 0.05$). *Significant difference from the *Pre* for the DHEA-treated groups.

Results

DHEA-S

Morning fasted DHEA-S level in all three groups, as measured before treatments and 14 h (overnight) after the last oral supplementation, are shown in Fig. 1. Oral DHEA administration significantly elevated serum DHEA level by approximately 3 folds ($P < 0.05$). Resistance exercises did not affect DHEA-S level.

OGTT

The OGTT result is shown in Table 1A. A resistance exercise with or without DHEA administration during the recovery did not affect a fasting glucose level. Resistance exercise, DHEA treatment, and a combination of both significantly lowered the glucose level after a 75-g of oral glucose load. Therefore, glucose tolerance was significantly improved by the resistance exercise, DHEA administration and resistance exercise with DHEA supplementation ($P < 0.05$). No additive effect of exercise and DHEA administration was found.

Insulin Level during OGTT

An insulin result is shown in Table 1B. Fasting insulin level was not significantly affected by resistance exercise regardless whether DHEA was

Table 1. Oral glucose tolerance test (A) and insulin response (B). *E-pre*: before resistance exercise. *E-post*: after resistance exercise and followed by placebo supplementation. *ED-pre*: before both resistance exercise and DHEA administration. *ED-post*: after resistance exercise and followed by DHEA administration. *D-pre*: before DHEA administration. *D-post*: after DHEA administration. * significant difference from the *Pre* ($P < 0.05$).

(A)

Blood glucose (mg/dl)	Fasting	30-min	50-min	80-min
E-pre	98±2.3	174±8.4	160±10	149±9.3
E-post	96±2.2	150±10*	142±9.9	127±7.3*
ED-pre	95±3.2	166±4.9	169±12	155±10
ED-post	93±2.6	147±8.9*	129±11*	116±7.3*
D-pre	99±11	159±18	162±19	147±19
D-post	96±10	139±16*	126±15	113±13*

(B)

Serum insulin (μU/ml)	Fasting	30-min	50-min	80-min
E-pre	9.3±1.0	53.0±3.7	47.5±5.3	49.5±5.6
E-post	9.8±1.0	46.3±4.9	44.4±3.9	30.2±3.9*
ED-pre	13.8±2.2	48.3±2.7	62.6±5.0	50.7±6.9
ED-post	12.8±7.4	41.9±5.1	45.4±5.4*	40.5±5.9
D-pre	15.3±4.9	50.6±10	59.2±23	50.1±16
D-post	10.2±2.1	38.9±8.3*	34.7±7.4*	22.4±5.1*

treated or not. Resistance exercise with placebo also significantly lowered the insulin levels during OGTT at 80th minutes. Resistance exercise with DHEA also significantly lowered the insulin levels during OGTT at 50th min. DHEA administration without exercise did not affect fasting insulin level. Insulin levels at 30th, 50th, 80th minutes under glucose challenge were significantly lowered by the DHEA administration without resistance exercise ($P < 0.05$). Lowered glucose level with lower insulin levels indicated that the improvements in glucose tolerance by all these treatments were due to increased insulin sensitivity. No additive effect of exercise and DHEA administration was observed.

Blood Creatine Kinase (CK)

Blood CK levels before and after an acute bout of resistance exercise (first two days after exercise) are shown in Fig. 2. In the placebo group, resistance

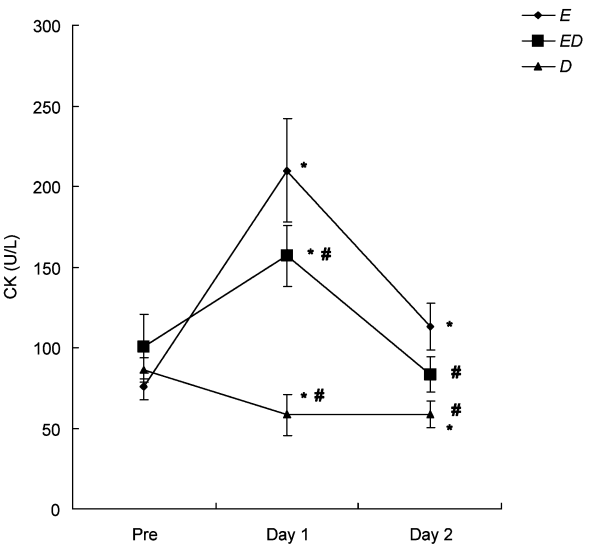

Fig. 2. Serum creatine kinase (CK) level before and after an acute bout of resistance exercise and/or DHEA administration. Pre: before treatments. *Day 1*: 1-day after treatments. *Day 2*: 2-day after treatments. #significant difference from the non-DHEA control on the same day. *significant difference from the *Pre* of the treatments ($P < 0.05$).

exercise significantly elevated blood CK level in the first day ($P < 0.05$). It was then declined within a 48-hour recovery period after this moderate resistance exercise, but remained significantly greater than the pre-exercise level ($P < 0.05$). In the exercise group with DHEA administration, the CK level was also elevated but was in less extent ($P < 0.05$). It was returned to a level that did not significantly different from the pre-exercise level within 48 hours. DHEA administration also significantly lowered the blood CK level in the non-exercise control subjects ($P < 0.05$).

Serum TNF-α Level

Figure 3 displays the serum TNF-α level before exercise and after an acute bout of resistance exercise. The resistance exercise significantly elevated the serum TNF-α level as determined 48 hours after the resistance exercise ($P < 0.05$). With DHEA administration after post-exercise recovery, the increased serum TNF-α level was significantly lowered, comparing with the level in the exercised group without DHEA administration, and did not differ from the pre-exercise value 48-h after exercise. DHEA administration without doing exercise did not affect CK level ($P < 0.05$).

Serum Lipids Profile

Table 2 displays the serum cholesterol and triglyceride results, respectively. The resistance

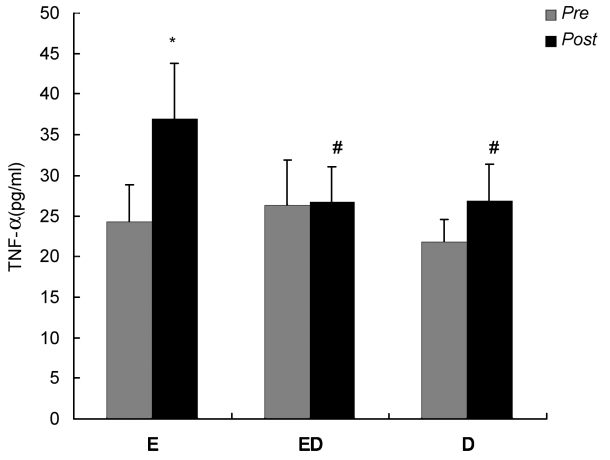

Fig. 3. Serum tumor necrosis factor- alpha (TNF-α) level before and after an acute bout of resistance exercise and/or DHEA administration. Pre: before treatments. *Day 1*: 1-day after treatments. *Day 2*: 2-day after treatments. #significant difference from the *Post* group for the E group as a non-DHEA control. *significant difference from the *Pre* of the treatment ($P < 0.05$).

Table 2. Serum cholesterol and triglyceride levels before and after an acute bout of resistance exercise and/or DHEA administration. #significant difference from the *E-post* group. *significant difference from the *Pre* ($P < 0.05$).

	Cholesterol (mg/dl)	Triglyceride (mg/dl)
E-pre	186±8.1	79±6.1
E-post	165±17	83±12
ED-pre	190±9.0	84±7.9
ED-post	113±4.6*#	71±5.6
D-pre	159±18	70±7.3
D-post	139±18#	72±8.2

exercise did not significantly affect serum cholesterol and triglyceride levels. However, with post-exercise DHEA administration during recovery, cholesterol level was significantly lowered, comparing with the pre-exercise level or with a single treatment alone ($P < 0.05$). Cholesterol in the DHEA group without exercise was also significantly greater than that in the other two groups ($P < 0.05$).

Discussion

We hypothesized that DHEA administration may be able to optimize the exercise effect on improving the insulin sensitivity and the glucose tolerance, based on the evidence that hyperinsulinemia occurred in parallel with a reduction of endogenous DHEA-S level in aging primates and humans (14, 20). However, according to our observation, the post-exercise DHEA administration did not further enhance the exercise training effect on insulin sensitivity and glucose tolerance. And yet intriguingly, the post-exercise DHEA administration significantly lowered the serum cholesterol and triglyceride (marginally significant) levels. This new finding suggests that the combination of exercise and DHEA, as a commonly used "anti-aging" intervention, could be a better method for improving lipid profiles in middle-aged women compared to either treatment alone. Whether chronically combined treatment can maintain same effect awaits further investigation.

Many previous studies have demonstrated that regular resistance training can enhance insulin sensitivity in skeletal muscle, and therefore contributes to the improvement in the whole body glucose tolerance and insulin sensitivity in human (13). In the current study, we found that an acute bout of resistance exercise was sufficient to improve glucose tolerance and insulin sensitivity in middle-aged women, and this effect can last for 48 hours following a single bout of resistance exercise training. Although it is generally thought that the effect of exercise training on insulin sensitivity is transient and cannot last for more than 24 hours (6, 13), most of the previous studies were performed in the form of concentric exercise. In contrast to these previous studies, the subjects of the present study performed dynamic exercise with alternated concentric and eccentric contractions, which confers the advantage that greater muscle fiber can be recruited, compared with the concentric exercise alone. The degree of training-induced improvement in glucose tolerance and muscle insulin sensitivity is generally known to related to exercise intensity or number of muscle fiber recruitment (5). This result therefore suggests that resistance exercise can be a good option for maintaining a better glycemic control to healthy middle-aged women.

In the past, insulin resistance or hyperinsulinemia has been implicated as a pathogenic origin for development of dyslipidemia, based on the correlational evidence that the abnormal lipid metabolism in an adult which is generally occurred in parallel with development of insulin resistance (19). However, we must note that correlation doesn't mean causal association. Apparently, our result that the improvement in insulin sensitivity by resistance exercise without a significant change in cholesterol level was unable to support this causal association as suggested by Revean (19). In fact, the coexistence of hyperlipidemia and insulin resistance was commonly observed in obese population (4, 12), which doesn't necessarily mean that insulin resistance would lead to

development of hyperlipidemia. Both conditions may be commonly originated from development of obesity. It is generally known that exercise improves insulin sensitivity because it has dual effect on the direct improvement in skeletal muscle insulin sensitivity (acute effect) and eliminated adiposity (long-term effect) (13). In this study, we showed that a single bout of exercise could enhance skeletal muscle insulin sensitivity but it could not substantially reduced the body fat. This result pointed to a possibility that the blood lipid could be lowered by doing exercise only when a body composition or the degree of adiposity was substantially reduced.

In this study, the most striking finding was that the combined treatments of resistance exercise and DHEA administration markedly lowered the serum cholesterol level, whereas the resistance exercise with placebo intake did not generate the same result. The underlying mechanism accounted for this result could be that DHEA was eliminating those negative factors which were derived from resistance exercise detrimental to lipid metabolism. Although insulin sensitivity was improved by resistance exercise, TNF-α was elevated throughout the 48-hour recovery period in the placebo group (Fig. 3). This may potentially counteract the beneficial effect of exercise, particularly to the blood lipid metabolism. TNF-α is known to cause changes in blood cholesterol and triglyceride levels found in several pathophysiological conditions, including obesity, inflammation, and aging (10, 17). It is thus possible that the TNF-α action attenuated the benefit of resistance exercise, but post-exercise DHEA administration unmasked the beneficial effect of exercise by suppressing or removing the exercise-induced TNF-α generation (Fig. 3). This cytokine can induce cholesterol synthesis and the secretion of lipoproteins in liver resulting in hypercholesterolemia (9). Administration of TNF-α to mice causes cholesterol to increase by approximately 20% (11). A pretreatment of mice with anti-TNF antibodies blocked the effect of lipopolysaccharide (LPS) on serum cholesterol and triglyceride levels, hepatic cholesterol and fatty acid synthesis, and a hepatic HMG-CoA reductase activity (16). These findings indicate that the method to eliminate exercise-induced TNF-α production may be beneficial to enhance the exercise effect on lipid metabolism.

The fact that only a combination of resistance exercise and DHEA administration showed an improvement in blood lipid profile implied that a combination of exercise and an anti-aging treatment is a better intervention for preventing age-associated dyslipidemia in middle-aged women. This result also suggested that a regular exercise alone is essential but not sufficient for generating a full beneficial effect on metabolic fitness. Exercise-derived damage could be a confounding factor that suppresses the beneficial effect of exercise, particularly for the patients with slower rate of recovery in greater age level. Asp *et al.* (1) previously demonstrates that a prolonged and vigorous eccentric muscle contraction could impair glycogen synthesis of the exercised muscle, indicating that a heavy exercise can cause adverse effect to the metabolic function of the muscle. In the current study, our data further showed that TNF-α and CK levels was elevated by a resistance training (Fig. 2; Fig. 3). Removing this side effect of resistance exercise with DHEA administration could be one way for generating a better outcome on the metabolic function. In addition, the capability to exercise is fundamental for an individual to maintain metabolic fitness by doing exercise, which is known to gradually decline with age. It has been suggested that the reduced exercise capability with advanced age was associated with reduction in adrenal production of DHEA (2), and DHEA replacement was found to improve exercise capacity in middle-aged women. For this high-risk group on metabolic disorders, prescribing an optimal exercise protocol with physiological dosage of DHEA, can be a better solution for the purpose of chronic disease prevention.

Conclusion

The current study found that, in middle-aged women, serum cholesterol and triglycerides were lowered by the resistance exercise with DHEA administration during recovery, but this change was absent in the exercise with placebo and the DHEA sedentary groups. The beneficial effect of post-exercise DHEA administration appeared to be related to its effect on reducing the exercise-induced muscle damage and serum TNF-α. In addition, glucose tolerance and insulin sensitivity can be significantly improved by an acute bout of resistance exercise, but was not further enhanced by the post-exercise DHEA administration.

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