Effects of Oral Contraceptives on Glucoregulatory Responses to Exercise

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Some of the effects of oral contraceptives (OCs) to alter glucoregulation may be ameliorated by exercise. To test this premise, the effects of acute aerobic exercise on postprandial glucose, insulin, and C-peptide responses (area under the curve [AUC]) were measured in 8 users of low-dose estrogen and progestin OCs (OC^+) and 10 women not using OCs (OC^-). They completed 2 randomly ordered intervention trials: (1) aerobic exercise on 3 consecutive days with a 2.5-hour, 75-g oral glucose tolerance test (OGTT) on day 4, and (2) no exercise for 3 days prior to the OGTT (control trial). The exercise was 50 minutes of treadmill walking at 70% $\dot{V}O_{2max}$. The groups were similar in age (27 ± 3 years), waist-to-hip ratio (0.74 ± 0.01), and cardiorespiratory fitness (32.5 ± 1.6 mL · kg body mass^{-1} · min^{-1}). Fasting plasma glucose, C-peptide, and insulin levels were similar ($P > .05$) between groups in the control trial. In both trials, $glucose_{AUC}$ was significantly greater (13%, $P < .05$) in OC^+. Exercise resulted in a significant ($P < .05$) decrease in fasting plasma glucose and insulin, $insulin_{AUC}$, $glucose_{AUC} \times insulin_{AUC}$, and $C\text{-}peptide_{AUC}$ in both groups, suggesting enhanced insulin action and/or reduced pancreatic insulin secretion. Hepatic insulin extraction ($[C\text{-}peptide_{AUC} - insulin_{AUC}]/C\text{-}peptide_{AUC}$) was increased following exercise only in OC^+. Thus, insulin action was enhanced in response to exercise in young sedentary women independent of OC use. The mechanisms for the acute exercise effect on insulin action may be different in OC users compared with normally menstruating women.

SOME OF THE health risks associated with oral contraceptive (OC) use, such as thromboembolic events and dyslipidemia, have diminished since the introduction of reduced doses of ethinyl estradiol (<50 μg/d) and less androgenic progestins.[1-3] These OCs effectively suppress the increase in ovarian hormones that normally occurs during the luteal phase of the menstrual cycle. Nevertheless, deterioration in glucose tolerance continues to be evident among low-dose OC users[4-7] and has been attributed to a combination of reduced peripheral insulin action[8] and glucose effectiveness with inadequate pancreatic β-cell compensation.[4] Furthermore, OCs may interfere with contraction-induced GLUT4 glucose transport as suggested by the ovariectomized rat model.[9]

Exercise may, however, ameliorate some of the effects of OCs to alter glucoregulation. In a cross-sectional study,[10] OC users who exercised regularly had significantly lower insulin and C-peptide responses (area under the curve [AUC]) to an oral glucose challenge than sedentary OC users. In this same study, the insulin and C-peptide responses were similar in exercising OC users and nonusers. Together, these comparisons suggest that regular exercise may counteract deleterious effects of OCs on insulin action or secretion.

The improvement in insulin action in response to aerobic exercise is short-lived, lasting about 48 hours. The insulin AUC in response to an oral or intravenous glucose challenge was significantly reduced 12 to 24 hours after acute exercise perturbations in sedentary, normoglycemic young women and men[11-14] and glucose-intolerant individuals.[15] Reduced postprandial insulin AUC following exercise may be explained by enhanced insulin action, reduced insulin secretion, and/or increased insulin clearance[16] and thus may counteract the potentially deleterious effects of OCs on these functions, as suggested by Godsland.[10]

To test the premise that regular exercise compensates for alterations in insulin action and secretion associated with OC use, we compared postprandial glucose, insulin, and C-peptide AUCs in sedentary OC users and nonusers following 2 randomly ordered trials of exercise or rest (control condition). We hypothesized that in response to an oral glucose challenge (1) insulin action would be enhanced 12 to 15 hours after the acute aerobic exercise stimulus, independent of OC use; and (2) insulin secretion would be reduced following the exercise stimulus, independent of OC use. Secondarily, we investigated alterations in hepatic insulin clearance in response to exercise and OC use.

SUBJECTS AND METHODS

Subjects

The study was approved by the Human Subjects Review Committee of Texas Woman's University. Participants were recruited using flyers posted on the campus. Twenty healthy, sedentary women aged 18 to 43 years provided written informed consent to participate in the study and completed the protocol. Participants were not obese, had no personal history of diabetes or cardiovascular disease, did not smoke, and did not engage in regular (≥2 times per week) endurance or strength training during the study and for 3 months prior to the study. Euglycemia (capillary whole-blood glucose < 110 mg/dL or 6.1 mmol/L) was verified by fingerstick blood sample screening after a 12-hour fast. Participants were grouped based on OC use. OC^+ were defined as those women who had been continuously using the same low-dose estrogen (<50 μg) and progesterone (mono- or triphasic) formulation for ≥1 year. OC^- were eumenorrheic women who had not used OCs for more than 1 year.

Testing Schedule

At least 1 week following a maximal treadmill exercise test, the participants completed the first of 2 randomly ordered trials of exercise or rest (control condition). In the exercise trial, participants completed submaximal exercise sessions on 3 consecutive days followed on the fourth day by an oral glucose tolerance test (OGTT). During the control trial, no exercise intervention took place in the 48 hours prior to the

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OGTT. Abstention from physical activity was verified using a questionnaire completed just prior to the control OGTT. Approximately 4 weeks separated the first and second trials. For OC^-, each trial was completed during the luteal phase of the menstrual cycle (17 to 23 days after the self-reported onset of menses), when both estradiol (E_2) and progesterone (P_4) levels would be expected to be elevated compared with the other phases of the menstrual cycle. For OC^+, the OGTT took place during days 15 to 21 of the pill cycle, with day 1 corresponding to the beginning of a new pill pack. In this phase of the pill cycle in OC^+, the potent exogenous hormones were expected to suppress endogenous levels of E_2 and P. Thus, the between-group comparisons were made under conditions where gonadotropin levels should be similarly suppressed due to high levels of either endogenous (OC^-) or exogenous (OC^+) E_2 and P_4.[17,18]

Maximal and Submaximal Exercise

The measurement of maximal aerobic capacity ($\%\dot{V}O_{2max}$) has been described previously.[19]. The $\dot{V}O_2$ responses during the maximal test were used to establish the submaximal exercise intensity. Submaximal exercise was performed in the laboratory between 3 PM and 7 PM on 3 consecutive days. Each exercise session consisted of walking for 50 minutes at 94 $m \cdot min^{-1}$ with the elevation adjusted to elicit a relative exercise intensity of 70% of $\dot{V}O_{2max}$. On the first day of exercise, $\dot{V}O_2$ was measured for 5 minutes at the start of exercise and during minutes 20 to 25 and 40 to 45 to verify the exercise intensity. The treadmill speed and grade on subsequent days of exercise were the same as those established on the first day. During all submaximal exercise sessions, heart rate was monitored via telemetry (Polar Monitor Model 61214; Country Technology, Gays Mill, WI). For the control trial, all participants reported to the laboratory between 3 PM and 7 PM the day prior to the OGTT.

Glucose Tolerance Testing

Participants returned to the laboratory for an OGTT 15 to 18 hours after the completion of the rest and exercise trials. All OGTTs commenced between 7 AM and 9 AM with the participants fasted for 12 to 15 hours. A catheter was inserted into an antecubital vein. Baseline (zero minute) blood samples were drawn into EDTA tubes for analyses of glucose, insulin, C-peptide, E_2, and P_4. Participants then drank a 75-g glucose solution (Tru-Glu 100; Fisher Scientific, Pittsburgh, PA). Additional blood samples were drawn at 30, 60, 90, 120, and 150 minutes after glucose ingestion for analyses of glucose, insulin, and C-peptide. All samples were gently mixed and then centrifuged at 4°C and 2,500 rpm for 10 minutes. A small amount of plasma was immediately analyzed for glucose with a 2300 Stat Plus Glucose/Lactate Analyzer (Yellow Springs Instruments, Yellow Springs, OH). The remaining plasma was stored at −80°C. Plasma insulin and C-peptide were analyzed by radioimmunoassay (RIA) using Coat-a-Count Insulin Kits and Double Antibody C-Peptide Kits (Diagnostic Products, Los Angeles, CA). In our laboratory, the intra- and interassay coefficients of variation for all hormones were less than 11.5%. Plasma E_2 and P_4 were determined via RIA (Diagnostic Products). For each assay, all samples from the same individual were analyzed using kits with the same lot numbers. A 10-detector gamma counter (RIASTAR 5410; Packard Instruments, Meriden, CT) was used for all RIAs.

Dietary Records

The participants were instructed to consume a diet of at least 150 g carbohydrate/d for the 3 days prior to each OGTT and to record their dietary intake on these days. The women were provided with photocopies of their food records from the first trial, and they were asked to repeat this diet for the 3 days prior to the second OGTT. Diet records were analyzed for intakes of energy and macronutrients using computer software (Nutritionist IV; N-Squared Computing, San Bruno, CA). Each participant was provided with the same evening meal (approximately 720 kcal containing 50% carbohydrate, 20% protein, and 30% fat) prior to each OGTT.

Body Composition Measurements

Body mass index (BMI) was derived from weight measurement to the nearest 0.1 kg using a Detecto-Medic scale (Detecto Scales, Brooklyn, NY) and height measured to the nearest 0.1 cm using a stadiometer (Perspective Enterprises, Kalamazoo, MI). The waist-to-hip ratio was derived from the minimum waist circumference (narrowest circumference of the torso) and maximum hip circumference (the greatest protrusion of the buttocks) with the participant in a standing position. Duplicate measures were made using a nonstretch, spring-loaded fiberglass tape. The average of duplicate measures was used in data analysis. Waist circumference was also used independently as an indicator of total abdominal fat. Subcutaneous adiposity was described as the sum of skinfold measurements of the triceps, suprailiac, and thigh as described by Pollock et al.[20] Three readings at each site within 1.0 mm were averaged and then summed.

Calculations and Statistics

The integrated AUCs for glucose, insulin, and C-peptide were calculated using the trapezoidal rule. $Insulin_{AUC}$ and $C\text{-}peptide_{AUC}$ were used as measures of insulin action and insulin secretion, respectively. These physiologic responses were also used to derive the product of the insulin and glucose AUC ($Ins_{AUC} \times Glu_{AUC}$), an index of whole body insulin action[21] and an index of fractional hepatic extraction of insulin (FHEI; $[C\text{-}peptide_{AUC} - insulin_{AUC}]/C\text{-}peptide_{AUC}$).[22]

Group comparisons of baseline body composition, cardiorespiratory fitness, and sex hormones were made using independent *t* tests. Two-way (OC use × trial) repeated measures analysis of variances (ANOVAs) were used to analyze fasting levels and the AUC for glucose, insulin, and C-peptide, $Ins_{AUC} \times Glu_{AUC}$, FHEI, and dietary data. Significance for each analysis was set at an α level of <0.05. Values are presented as the mean ± SE. Statistical calculations were made using SPSS (Chicago, IL) for Windows software (version 11.0).

RESULTS

Exclusions

Two women in the OC^+ group had impaired glucose tolerance (IGT; 120-minute OGTT plasma glucose ≥ 140 mg/dL or 7.8 mmol/L[23]) in the control trial, and 1 of these 2 OC^+ also exhibited IGT in the exercise trial. Data from the women with IGT were eliminated from further analyses, and the results below represent 8 OC^+ and 10 OC^-. The remaining OGTT data were normally distributed.

Subject Characteristics

OC^+ tended to have a larger BMI, waist circumference, and sum of skinfolds than OC^- (Table 1), although these differences were not statistically significant. The groups had similar maximal aerobic capacity. Each group achieved approximately 70% of $\dot{V}O_{2max}$ during submaximal exercise on 3 consecutive days with a trend towards higher intensity exercise in OC^- (75% ± 2% *v* 70% ± 1% $\dot{V}O_{2max}$; $P = .07$). Submaximal exercise heart rates were not significantly different in OC^+ and OC^- (149 ± 7 *v* 152 ± 3 bpm, respectively). Dietary intake was similar between groups and trials (data not shown).

OC^+ had been taking the same oral contraceptive formulation for 2.8 ± 1.7 years. The OC formulations used are listed

Table 1. Baseline Characteristics

	OC^+ (n = 8)	OC^- (n = 10)
Age (yr)	28.4 ± 3.2	26.7 ± 2.6
Height (cm)	163.8 ± 2.4	165.1 ± 1.5
Weight (kg)	66.4 ± 6.4	62.6 ± 2.9
BMI (kg/m^2)	24.7 ± 2.3	23.0 ± 1.2
Waist-to-hip ratio	0.74 ± 0.01	0.74 ± 0.02
Waist circumference* (cm)	77.0 ± 5.5	73.8 ± 2.4
Sum of skinfolds* (mm)	62.9 ± 5.0	55.9 ± 6.2
$\dot{V}O_{2max}$ (mL · kg body mass^{-1} · min^{-1})	33.1 ± 2.1	32.3 ± 1.2

NOTE. Values are means ± SE.
Abbreviations: OC^+, oral contraceptive users; OC^-, nonusers.
*n = 9 OC^-.

in Table 2. As expected OC^+ had significantly ($P < .001$) lower plasma concentrations of E_2 and P_4 (E_2, 84.4 ± 3.7 pmol/L; P_4, 1.3 ± 0.2 nmol/L) than OC^- (E_2, 333.7 ± 40.7 pmol/L; P_4, 20.7 ± 5.1 nmol/L), averaged across trials. In OC^-, E_2 and P_4 levels were indicative of the luteal phase of the menstrual cycle.

Fasting and Postprandial Glucose, Insulin, and C-Peptide

In the control trial, OC^+ had lower fasting glucose and 24% greater fasting insulin than OC^-, although these differences were not statistically significant. Fasting glucose and insulin were significantly reduced after exercise in both groups, with a trend for lower fasting C-peptide (Table 3).

The postprandial glucose responses were significantly greater in OC^+ than OC^- in the control (14%) and exercise trials (12%; Table 3). In OC^+, the insulin and C-peptide AUCs and $Ins_{AUC} \times Glu_{AUC}$ tended to be greater (12% to 17%) than OC^-, but none of these differences were statistically significant. The exercise effect was significant for $insulin_{AUC}$, $Ins_{AUC} \times Glu_{AUC}$, and $C\text{-peptide}_{AUC}$. Aerobic exercise resulted in an 18% and 15% reduction in $insulin_{AUC}$ in OC^+ and OC^-, respectively. A significant 15% reduction in $Ins_{AUC} \times Glu_{AUC}$ following exercise indicated enhanced whole body insulin action in both groups. The exercise effect was sufficient to reduce $insulin_{AUC,}$ and $Ins_{AUC} \times Glu_{AUC}$ in OC^+ to the levels of OC^- in the control condition. The magnitude of the reduction in $C\text{-peptide}_{AUC}$ was smaller in OC^+ (6%) than OC^- (14%). We found a significant interaction ($P < .05$) of OCs and exercise on estimated hepatic insulin clearance. In OC^+, FHEI was significantly greater ($P < .01$) after exercise than in the control trial (0.88 ± 0.01 *v* 0.86 ± 0.01, respectively), whereas no significant differences in FHEI were found within OC^- (0.88 ± 0.02 exercised; 0.87 ± 0.02 control).

DISCUSSION

Previous research[10] suggested that OC use and exercise had counterbalancing effects on insulin action, ie, that OCs deteriorate and exercise enhances insulin action. Because this premise was based on cross-sectional comparisons of sedentary and physically active women, we investigated the insulin responses to an oral glucose challenge using a controlled, acute exercise intervention in sedentary OC users and nonusers. OC^+ had significantly lower plasma E_2 and P_4 than OC^-, indicating the expected suppression of endogenous hormone secretion by OCs. As a result of studying women during the "luteal" phase of the menstrual or pill cycle, we achieved a comparison of high levels of endogenous versus exogenous hormones. The inclusion of women using various OC combinations precludes discussion of the effects of the type of progestins or ratio of progestins to estrogen on insulin action. Although OC use was self-selected by the subjects for at least 1 year prior to study entry, our data were not confounded by differences in body composition or cardiorespiratory fitness.

Our first hypothesis, that 3 consecutive days of aerobic exercise would enhance insulin action independent of OC use, was supported by significant reductions in the postglucose load insulin AUCs in response to the acute exercise stimulus in both OC^+ and OC^-. Greater postprandial glucose responses were found in OC^+ in both the control and exercise conditions, despite the removal of data from 2 individuals who met the clinical definition of IGT (2-hour postprandial hyperglycemia). The pattern of unchanged glucose AUC in the face of reduced insulin AUC after exercise concurs with previous acute exercise studies of healthy young women and men.[11,12,14,19] Further support for exercise-induced enhancement of insulin action was the significant reductions in $Ins_{AUC} \times Glu_{AUC}$ and fasting insulin in both groups.

Table 2. Oral Contraceptive Formulations Used by Participants

Type	No.	Trade Name	Hormone Dose	
			Ethinyl Estradiol	Progestin
Monophasics				
	2	Lo/Ovral	30 μg	Norgestrel 0.3 mg
	1	Ortho-Cept	30 μg	Desogestrel 0.15 mg
	1	Loestrin 1/20	20 μg	Norethindrone 1.0 mg
Triphasics				
	3	Ortho-Tricyclen	35 μg	Norgestimate 0.180 mg × 7 d
				Norgestimate 0.215 mg × 7 d
				Norgestimate 0.250 mg × 7 d
	1	Tri-Levlen	30 μg	Levonorgestrel 0.050 mg × 6 d
			40 μg	Levonorgestrel 0.750 mg × 5 d
			30 μg	Levonorgestrel 0.125 mg × 10 d

Table 3. Fasting and Postprandial Glucoregulatory Parameters in Oral Contraceptive Users (n = 8) and Nonusers (n = 10)

		Trials		Main Effects* *P* Values	
	OC Use	Inactive	Exercised	OC	Trial
Fasting concentrations					
Glucose (mmol/L)	OC^+	4.46 ± 0.11	4.35 ± 0.11	.38	.008
	OC^-	4.61 ± 0.08	4.46 ± 0.12		
Insulin (pmol/L)	OC^+	53.24 ± 8.28	44.08 ± 6.13	.34	.03
	OC^-	42.94 ± 5.32	37.39 ± 6.04		
C-peptide (nmol/L)	OC^+	653.0 ± 59.4	634.1 ± 60.9	.87	.07
	OC^-	688.4 ± 54.0	575.2 ± 48.3		
Postprandial responses					
Glucose AUC (mmol/L · min · 10^2)	OC^+	8.4 ± 0.4	8.4 ± 0.4	.03	.56
	OC^-	7.2 ± 0.3	7.4 ± 0.3		
Insulin AUC (pmol/L · min · 10^4)	OC^+	5.1 ± 0.5	4.2 ± 0.5	.65	<.001
	OC^-	4.5 ± 0.8	3.8 ± 0.7		
C-peptide AUC (nmol/L · min · 10^2)	OC^+	3.7 ± 0.2	3.5 ± 0.8	.18	.02
	OC^-	3.3 ± 0.3	2.9 ± 0.2		
$Ins_{AUC} \times Glu_{AUC}$ (U × 10^7)	OC^+	4.1 ± 0.3	3.5 ± 0.4	.38	.003
	OC^-	3.4 ± 0.7	2.9 ± 0.5		

NOTE. Data are means ± SE.

Abbreviations: OC^+, oral contraceptive users; OC^-, nonusers.

*For all parameters, interactions were not significant ($P > .05$).

Jensen and Levine[24] using an OGTT, and Godsland et al[25] using an intravenous glucose tolerance test (IVGTT), also found sustained elevations of postload glucose in OC users. Godsland et al[25] reasoned that sustained elevation of glucose levels in OC users resulted from greater insulin resistance. In a longitudinal study using stable isotope methodology, Suh et al[8] determined that the metabolic clearance of glucose was suppressed during an exercise bout at 65% of $\dot{V}O_{2peak}$ 4 months after initiating OCs. Therefore, our finding of a greater glucose response after the oral glucose challenge in OC^+, who had been using OCs for more than 1 year, may represent a decreased glucose metabolic clearance rate.

Mechanisms underlying the improvement in insulin action 24 hours after exercise are not well defined. Contraction-induced GLUT4 transporter gene expression in vastus lateralis was significantly elevated up to 3 hours after a single bout of cycling at 73% of $\dot{V}O_{2peak}$ for 60 minutes in untrained women and men.[26] In contrast, subcutaneous administration of physiologic doses of progesterone, alone or in combination with 17-β estradiol, to ovariectomized rats resulted in significantly diminished glucose uptake, glycogen content, and GLUT4 transporter protein content in red gastrocnemius muscle relative to sham-operated rats following 30 minutes of exercise.[9] Although neither of these experiments was conducted 12 hours after the exercise perturbation, they nevertheless illustrate opposing effects of acute aerobic exercise and exogenous estrogen and progestins on contraction-induced glucose transport systems. Alternatively, because the current studies were conducted 12 hours after the last bout of exercise, the improvements in insulin action may reflect upregulation of insulin-mediated GLUT4 glucose transport, as demonstrated in habitually trained women and men.[27] Tissue-level studies of GLUT4 transporter expression and activity measured 12 to 24 hours after the last bout of exercise, and in response to a glucose challenge, will be required to examine the interaction of OCs on contraction- and insulin-stimulated glucose transport.

In confirmation of our second hypothesis, the C-peptide AUCs in OC^+ and OC^- were significantly reduced following exercise. The reductions in postprandial insulin and C-peptide AUCs in response to an acute exercise stimulus in OC^+ were consistent with the smaller AUCs in physically active, as compared with sedentary, OC users in Godsland's cross-sectional study.[10] Because both the C-peptide and insulin responses decreased in the present study, it may be concluded that the acute exercise bouts elicited a reduction in pancreatic insulin secretion, as also observed by King et al.[16] However, peripheral insulin concentrations are the result of pancreatic secretion minus the extraction of insulin by splanchnic and extrasplanchnic tissues (ie, skeletal muscle).[28] The increase in FHEI with exercise specifically in OC^+, together with their smaller change in $C\text{-peptide}_{AUC}$ (6% *v* 14% in OC^-), supports the contention that the mechanism for their reduced postexercise insulin response includes enhanced hepatic insulin clearance. Kojima et al[29] have demonstrated a defect in whole body insulin clearance in OC users. Similarly, oral equine estrogen, but not transdermal estrogen, in doses that increased serum E_2 to levels comparable to the luteal phase, decreased whole body insulin clearance in postmenopausal women.[30] Thus, the target tissues of the exercise effect may be primarily skeletal muscle and pancreatic β cells in OC^- and skeletal muscle and hepatic tissue in OC^+. Indeed, the first pass hepatic metabolism of oral estrogen and progestin administration may result in pharmacologic effects on the liver that play a key role in altering insulin clearance. However, we interpret our results with caution due to the assumptions underlying the estimation of hepatic insulin clearance using peripheral C-peptide concentrations.[31] The introduction of effective transdermal contraception[32] offers the opportunity to ex-

plore the possibility that OCs may alter the saturation kinetics for hepatic insulin clearance.

We have demonstrated, within the limitations of the OGTT methodology, that an acute aerobic exercise intervention enhances insulin action in sedentary women using OCs. Our data support the premise that women who use OCs and engage in regular aerobic exercise may be protected from alterations in insulin action imparted by exogenous estrogen, progestins, or their interaction.

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