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Effect of a single vs multiple bouts of exercise on glucose control in women with type 2 diabetes☆

Tracy Baynard*, Ruth M. Franklin, Styliani Goulopoulou, Robert Carhart Jr, Jill A. Kanaley

Department of Exercise Science, Syracuse University, Syracuse, NY 13244, USA

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Abstract

The Surgeon General and Centers for Disease Control and Prevention have recommended that multiple bouts of exercise can be accumulated throughout the day in lieu of the more traditional single, longer bout of exercise. Yet, conclusive evidence does not exist suggesting these 2 training modes provide similar health-related benefits on metabolic control, especially in individuals with type 2 diabetes. The purpose of this study was to determine if differences exist in glucose control when preceded by one 30-minute or three 10-minute bouts of exercise in women with type 2 diabetes. Nine individuals with type 2 diabetes (53 ± 6 years old) and 6 control women (49 ± 4 years old) completed 3 randomly ordered oral glucose tolerance tests (OGTTs). Two of the OGTTs were preceded the day prior by moderate exercise (~60% of VO_{2peak}), either one 30-minute or three 10-minute bouts, whereas the third OGTT was used as a control day with no exercise performed 3 days prior. Glucose and insulin were measured every 30 minutes for 4 hours during the OGTT. Individuals with type 2 diabetes exhibited a greater overall glucose response than the controls ($P < .05$), but the glucose response to the OGTT was not different between the 3 conditions within each group (2-hour glucose: multiple bout, 14.3 ± 3.2 vs 5.0 ± 1.7; single bout, 14.1 ± 3.0 vs 4.7 ± 1.5; control day, 14.6 ± 2.7 vs 4.9 ± 4.9 mmol/L). Glucose area under the curve analysis resulted in similar findings. As expected, the group with type 2 diabetes had greater fasting insulin levels compared with the control group for all exercise conditions (multiple bout: 4.5 ± 1.2 vs 0.3 ± 0.2; single bout: 6.4 ± 1.6 vs 0.9 ± 0.4; control day: 5.7 ± 1.8 vs 1.5 ± 0.6 pmol/L; $P < .05$). Exercise or no exercise did not alter the insulin response to the OGTT for either group. Despite a higher glucose response to the glucose load in T2D, an acute exercise bout (single or multiple bouts) did not appear to alter glucose control the following day in either the individuals with type 2 diabetes or the control group.

1. Introduction

Moderate to vigorous exercise has been demonstrated to elicit improvements in skeletal muscle glucose metabolism, primarily through increased expression of the glucose transporter GLUT-4 and adaptations of other enzymes involved with glucose phosphorylation and oxidation [1-6]. Not only have skeletal muscle contractions been found to circumvent insulin-mediated glucose uptake via contraction-specific intracellular pools of GLUT-4 [7], but the effect of exercise has also been found to increase insulin-mediated glucose uptake several hours (2-24 hours) after the exercise bout [8-12]. In fact, the improvement in insulin-mediated glucose uptake with exercise training is largely thought to occur because of the effect of the last bout of exercise [6,13,14] rather than the chronic effect of training itself, as benefits in glucose tolerance have been found to disappear several days after the last exercise session in humans [9,11]. Although much of the research in this area has focused on healthy individuals [10,11] and animal models [3,12,15], few studies have involved individuals with type 2 diabetes.

Individuals with type 2 diabetes are primarily glucose intolerant because of a high level of insulin resistance. Thus, regular exercise has often been included as part of the lifestyle interventions recommended by physicians to this population. The primary goal for an exercise intervention is, of course, an end point of improved glucose tolerance or increased insulin sensitivity. Although little research exists regarding acute exercise and type 2 diabetes, a few studies have found that a single acute session of aerobic exercise, and even resistance exercise, beneficially improves glucose tolerance and/or insulin sensitivity in individuals with type 2 diabetes [9,16-18]. Kennedy et al [16] has even observed in

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* Corresponding author. Tel.: +1 315 443 2114; fax: +1 315 443 9375.
E-mail address: tbaynard@syr.edu (T. Baynard).

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patients with type 2 diabetes an increase in exercise-induced GLUT-4 translocation after a single bout of exercise cycling for 45 to 60 minutes at 60% to 70% peak oxygen uptake.

Yet, the positive findings associated with acute exercise are generally observed with higher exercise intensities or sessions of longer duration (ie, $\geq$1 hour). For nearly a decade, the Surgeon General and the Centers for Disease Control and Prevention, in conjunction with the American College of Sports Medicine and the American Heart Association, have recommended that individuals should be exercising at a moderate intensity all or most days of the week for 30 minutes or more [19]. What makes these guidelines unique is that the activity can be accumulated throughout the day (ie, shorter sessions) to attain the 30-minute or greater goal. These physical activity guidelines are generally far below the type of intensity and duration commonly found in many research experiments involving aerobic exercise. Since the report debuted, little research has been conducted involving the effects of accumulated exercise on health related parameters. In particular, very little research exists on fractionated exercise in special populations, such as type 2 diabetes, where exercise is generally included as a first line of treatment.

Therefore, the purpose of this study was to determine if single or multiple bouts of exercise differentially affect glucose tolerance in individuals with type 2 diabetes compared with age-matched healthy individuals. We hypothesized that the fractionated exercise condition would yield the same improvements in glucose control as a single exercise session in the individuals with type 2 diabetes and a healthy control group. In addition, both exercise conditions would yield increased glucose control compared with the non-exercise condition.

2. Methods

2.1. Subjects

Fifteen sedentary women (42-60 years old) volunteered for study participation, of which 9 were obese participants with type 2 diabetes, and 6 were non-obese, healthy nondiabetic women. Obese women had a body mass index (BMI) greater than 30 kg/m^2 and non-obese women had a BMI less than 24 kg/m^2. Subject characteristics are presented in Table 1. Subjects with type 2 diabetes were diagnosed by their physician using the American Diabetes Association criterion [20]. All participants completed a medical screening questionnaire before enrollment. Exclusionary criteria included smoking, known cardiovascular disease, peripheral vascular, renal, hepatic, pulmonary, adrenal, or pituitary disease, or untreated hypo- or hyperthyroidism, and significant hypertension (>160/100 at rest). Individuals on insulin, β-blockers, or individuals participating in regular physical activity (aerobic or resistance) during the previous 6 months were also excluded from the study. Participants with type 2 diabetes continued their hypoglycemic medications as prescribed for all testing and exercise days, but had to be on a stable dose for the previous 2 months or longer. In total, 4 women took their oral hypoglycemic medications in the morning, 3 took their medication in the evening, and 1 participant took her medication both in the morning and evening. Women of perimenopausal status were not included to control for hormonal fluctuations associated with perimenopause. All premenopausal women (2 with type 2 diabetes and 4 controls) were tested during the follicular phase (days 1-10) of their menstrual cycle. Nine women (7 with type 2 diabetes and 2 controls) were postmenopausal, with 4 on hormone replacement therapy (3 with type 2 diabetes and 1 control). Oral hypoglycemic medications included metformin (n = 2), a combination of sulfonylureas and metformin (n = 4), a combination of sulfonylurea and thiazolidinediones (n = 1), and a combination of metformin and thiazolidinediones (n = 2). Written informed consent was obtained from the participants, and the study protocol was approved by the Syracuse University Institutional Review Board.

Table 1
Descriptive data

	Type 2 diabetes (n = 9)	Non-obese (n = 6)
Age (y)	53 ± 2	49 ± 2
Height (cm)	160.3 ± 1.8	163.9 ± 1.7
Weight (kg)	93.1 ± 5.3	59.4 ± 2.1*
BMI (kg/m^2)	36.1 ± 1.8	22.0 ±0.6*
Waist (cm)	115.5 ± 3.1	74.2 ± 2.6*
% Body fat	45.0 ± 1.6	31.0 ± 0.9*

Values are mean ± SEM.
* $P < .0001$ between groups.

2.2. Design

Subjects came to the laboratory on 4 occasions. On the first visit, all participants completed a graded exercise test for measurement of aerobic capacity and to look for contraindications for exercise. All subjects then came in for 3 study days, which included a 4-hour oral glucose tolerance test (OGTT). On the day before the study day, the subjects came to the laboratory to exercise: (1) a single 30-minute bout of exercise, (2) three 10-minute bouts of exercise, and (3) no exercise. The exercise conditions were completed in random order. Both exercise bouts were completed on a treadmill at 60% to 65% of maximal oxygen consumption (V_{O_2}).

2.3. Peak aerobic capacity

Aerobic capacity was assessed on a treadmill using a walking protocol previously described [21]. Briefly, starting at 2.5 mph for 2-minute speed was increased 0.5 mph every 2 minutes until 3.5 mph was reached, after which grade was increased by 2% every 2 minutes until voluntary exhaustion. Metabolic data were collected and analyzed using a breath-by-breath open circuit spirometer (Cosmed Quark b^2, Rome, Italy). Heart rate (HR) was obtained from a standard 12-lead

electrocardiogram that was monitored by a cardiologist for any abnormalities. An electrocardiographic recording and blood pressure were obtained once every stage, at maximal exercise, and during recovery at minutes 1, 3, and 6. In addition, rating of perceived exertion was obtained once every stage and during peak exercise.

2.4. Body composition

Air plethysmography using the Bod Pod (Life Measurements Inc, Concord, Calif) was used to assess the percentage of body fat. Waist and hip circumferences were measured and BMI (kg/m^2) was calculated.

2.5. Exercise conditions

The participants performed the 3 conditions (1-30 minutes, 3-10 minutes, no exercise), in random order, with a minimum of 14 days between each condition. The exercise conditions consisted of exercising at 60% to 65% of VO_{2peak}. The single 30-minute exercise bout was performed at 5:00 PM, with the three 10-minute sessions performed at 8:00 AM, 12:00 PM, and 5:15 PM. This design was used to ensure the end of each exercise day occurred at approximately the same time of day. The participants had oxygen uptake, HR, and rating of perceived exertion measured during each entire exercise session to accurately ascertain the correct exercise intensity. Heart rate was measured using a Polar heart rate monitor (Woodbury, NY). For the no-exercise condition, all subjects were asked to refrain from exercise outside normal activities of daily living for 3 days before testing. In addition, all participants were also asked to limit their physical activity to activities of daily living for a minimum of 3 days before the actual exercise sessions.

2.6. Oral glucose tolerance test

After an overnight fast, the OGTTs were performed at 07:30 AM for each of the 3 conditions. A Teflon catheter was placed into the antecubital vein to obtain serial blood samples. Blood samples were used to measure blood glucose concentrations and insulin levels. Once fasting blood samples were drawn, the participants were instructed to consume a 75-g dextrose solution in a 3-minute period (Trutol 75, East Providence, RI). Blood draws were then performed every 30 minutes for 4 hours. Other than the exercise intervention, no regular exercise was performed for 3 days before the OGTT.

2.7. Blood analyses

Whole blood glucose concentrations were analyzed using the glucose oxidase method immediately after each blood draw with a YSI 2300 STAT glucose analyzer (Yellow Springs, Ohio). Whole blood was collected in tubes containing EDTA and centrifuged at 4°C at 2300 rpm, with the plasma aliquoted and stored at −80°C for later analysis. Insulin concentrations were analyzed in duplicate using commercial radioimmunoassay kits (Diagnostic Products Corporation, Los Angeles, Calif). The 3 study conditions from individual subjects were batched and analyzed in the same assay. The intra-assay coefficient of variation was 6.75% and the inter-assay coefficient of variation was 11.8%. Insulin sensitivity was calculated using the Oral Glucose Insulin Sensitivity (OGIS) model by Mari et al (*Diabetes Care* 2001).

2.8. Statistical analyses

Descriptive data of the 2 groups were analyzed using independent *t* tests. A 2-way analysis of variance (ANOVA) with repeated measures (group [2] × condition [3]) was used to determine if significant differences existed between the 3 exercise conditions for the dependent measurements. Significance was set at an α equal to .05. SPSS (v. 11.5) (Chicago, Ill) was used for all statistical analyses. GraphPad Prism (v. 3.02) (San Diego, Calif) was used to calculate area under the curve (AUC) for both glucose and insulin. Values are reported as mean ± SEM.

3. Results

There were no statistically significant differences in age or height between groups. Participants with type 2 diabetes were heavier and had a higher BMI, waist circumference, and percentage of body fat compared with the non-obese group (Table 1). There were no statistical differences between groups for peak HR (type 2 diabetes vs non-obese) (164 ± 5 vs 177 ± 5 beats per minute) and maximal ventilation (63.5 ± 4.8 vs 78.5 ± 5.3 L/min). The non-obese group exhibited a greater VO_{2peak} vs the group with type 2 diabetes (33.4 ± 0.6 vs 17.7 ± 0.6 mL/kg per minute, respectively) ($P < .0001$). After adjusting for differences in lean body mass, VO_{2peak} remained higher for the non-obese group compared with the group with type 2 diabetes (48.8 ± 1.3 vs 34.2 ± 1.3 mL/kg of lean body mass per minute, $P < .05$).

During the submaximal exercise bout, both groups exercised at the same relative intensity for all exercise

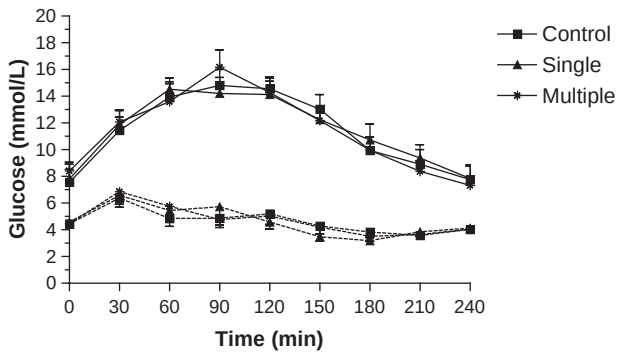

Fig. 1. Glucose concentrations (mmol/L) during an OGTT. Solid lines represent the obese participants with type 2 diabetes and the dashed lines represent the non-obese control group. Significant group effect ($P < .05$), with type 2 diabetes having greater glucose concentrations at all time points. No difference between any of the 3 conditions was observed.

Table 2
Glucose AUC

	Glucose AUC (mmol/L per minute)	
	Type 2 diabetes	Non-obese*
Control condition	2828 ± 177	1115 ± 217
Single bout	2847 ± 174	1088 ± 213
Multiple bouts	2579 ± 280	1139 ± 344

Values are mean ± SEM.

* $P < .0001$, significantly different from obese type 2 diabetes. No difference between conditions.

conditions, with no differences between groups (patients with type 2 diabetes, 62% VO_{2peak}; non-obese, 61% VO_{2peak}). The non-obese group exercised at a higher relative VO_2 on both exercise conditions (multiple: 20.3 ± 0.7 mL/kg per minute, single: 20.7 ± 0.7 mL/kg per minute) compared with the group with type 2 diabetes (multiple: 11.0 ± 0.4, single: 10.9 ± 0.3) ($P < .0001$). Energy expenditure (kJ) was calculated for the single exercise session and for the sum of the three 10-minute bouts using the oxygen consumption values obtained during exercise from the metabolic cart. No differences between exercise days were found for either group (data not shown). Exercise energy expenditure was higher in the non-obese group compared with the group with type 2 diabetes (697.2 ± 10 vs 621.6 ± 10 kJ, respectively), yet this was not significant.

Fasting glucose concentrations were higher for the group with type 2 diabetes compared with the non-obese group ($P < .05$) for all 3 conditions (Fig. 1) and the glucose concentrations were greater at each time point of the OGTT for the group with type 2 diabetes vs the non-obese group ($P < .05$), with no differences between conditions observed for either group (Fig. 1). No differences between conditions were observed for glucose AUC (mmol/L per minute), although a significant group effect was observed ($P < .0001$) (Table 2).

Fasting insulin concentrations were significantly greater in the group with type 2 diabetes vs the non-obese group for both exercise conditions and the control day ($P < .05$) (Fig. 2). In addition, separate analyses of each group (type 2 diabetes and non-obese) found that no differences in fasting

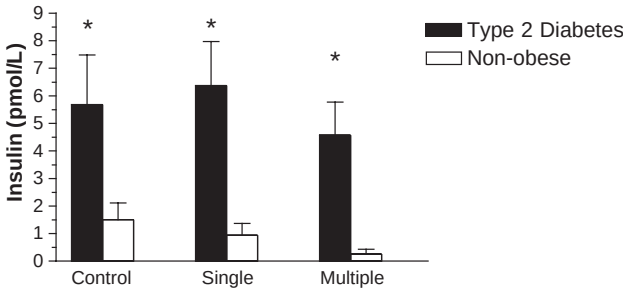

Fig. 2. Fasting insulin concentrations (pmol/L) for type 2 diabetic and non-obese women. Asterisk indicates $P < .05$, significantly greater insulin concentrations for the group with type 2 diabetes compared with non-obese group on the control day and each exercise condition (single or multiple bouts).

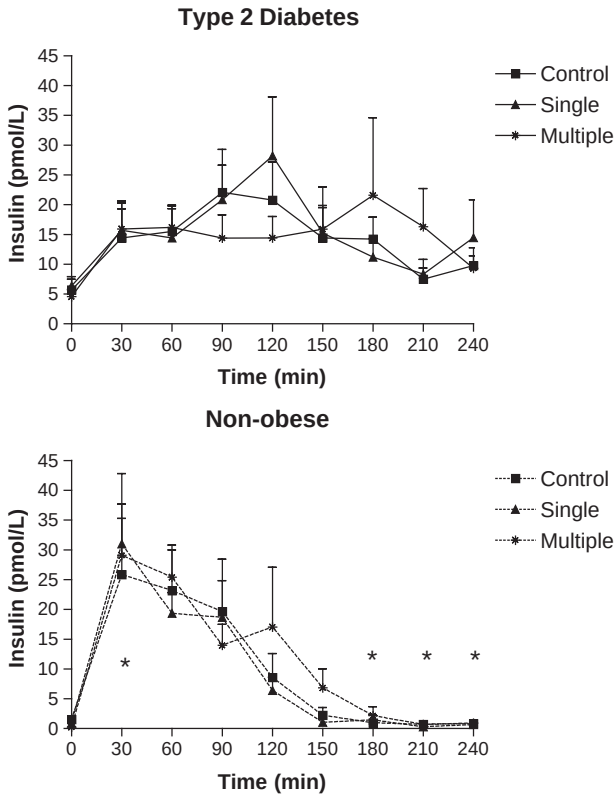

Fig. 3. Insulin concentrations (pmol/L) during an OGTT. Asterisk indicates $P < .05$, significant time × group effect observed, with differences observed between groups at 30, 180, 210, and 240 minutes. No differences between conditions were observed during the OGTT.

insulin concentrations existed between exercise days or the control day (Fig. 2). A significant time by group interaction was found for insulin levels during the OGTT ($P < .05$) (Fig. 3). Analysis of the insulin concentrations for each time point of the OGTT revealed that differences between groups existed at the 30-, 180-, 210-, and 240-minute time points ($P < .05$) (Fig. 3). No effect of exercise condition was found for insulin concentrations during the OGTT. In addition, no interaction or main effect for insulin AUC was observed (data not shown). Insulin sensitivity, as derived by the OGIS model, was significantly greater in the non-obese group compared with the group with type

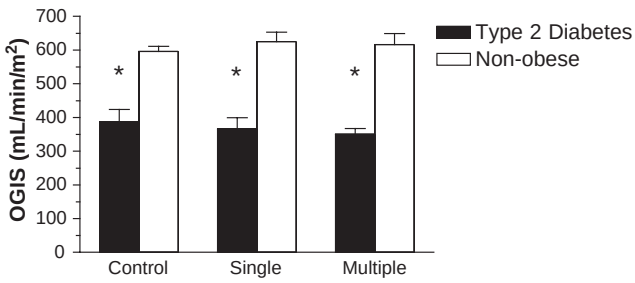

Fig. 4. Insulin sensitivity derived from the OGIS model. Asterisk indicates $P < .0001$, significant group effect; type 2 diabetes vs non-obese control group.

2 diabetes ($P < .0001$) (Fig. 4), but no differences were found between exercise conditions.

4. Discussion

This study yielded several interesting findings. First, single or multiple bouts of aerobic exercise of moderate intensity had no impact on glucose tolerance or insulin sensitivity the following morning. Secondly, the control condition (no-exercise day) was not different from either of the 2 exercise conditions with regard to glucose tolerance or insulin sensitivity, which contradicts earlier findings, which have been primarily conducted in non-obese individuals.

The primary aim of our study was to determine if the exercise (accumulated or continuous) recommendations by the Centers for Disease Control and Prevention are sufficient in improving glucose control in type 2 diabetes. We found no effect of the different exercise conditions on glycemic control. Furthermore, in contrast to other studies, we also found no difference between the exercise days and the no-exercise day. It is possible that the exercise intensity (or duration) chosen in our study was not high enough to elicit significant changes in glucose control in either group. Braun et al [17] investigated the effect of exercise intensity in women with type 2 diabetes and observed that only the insulin response to a meal test after 4 bouts of high-intensity exercise over 2 days (75% Vo_{2peak}) was greater than 4 bouts of low-intensity exercise (50% Vo_{2peak}) over 2 days. The total energy expended associated with the exercise bouts equaled 2100 kJ [17]. They also noted that the meal test did not alter the plasma glucose response in response to either exercise condition, including a no-exercise condition [17]. This supports our findings that moderate intensity exercise may not alter plasma glucose values. Although our study used a greater intensity than in the study of Braun (60% vs 50%), we still failed to demonstrate an increased insulin response to exercise compared with the no-exercise condition, regardless of similar sample sizes. Two important differences should be noted between our findings and those of Braun et al [17]. First, the energy expended was significantly greater in the study of Braun (2100 vs ~651 kJ), suggesting it may be necessary to reach a threshold of energy expenditure to reap the insulin-lowering effects of exercise, which has not been investigated. Secondly, it is difficult to ascertain the acute effects of *one* exercise session in the study of Braun et al [17], as 4 bouts of exercise were performed over 2 consecutive days before the meal test, with the meal test in the study of Braun et al occurring 90 minutes immediately after the fourth exercise session. In contrast, our study conducted the OGTT approximately 14 hours after the last exercise bout. Yet, timing of the last exercise session and testing for glucose control are obviously important issues to be considered in future investigations.

It is widely accepted now that muscular contractions are able to bypass the insulin-stimulated cascade of glucose transport both in animal and human models [1,2,5,7], making exercise a desirable alternative for glucose uptake in individuals with impaired glucose uptake, such as type 2 diabetes. For instance, Heath et al [10] found that after a 10-day detraining period in endurance athletes, one single bout of exercise similar in intensity and duration to their normal training sessions elicited a decrease in plasma glucose and insulin levels similar to their initial "trained" levels. Despite these promising findings in healthy young trained individuals, we did not observe any decrease in glucose or insulin concentrations in our subjects after a single exercise session, which is very likely related to the large differences in energy expended between sedentary and trained subjects.

Rogers et al [22], studying a group with type 2 diabetes, found that 7 days of aerobic exercise training at 68% of Vo_{2peak} resulted in improvements in glucose tolerance (36% decrease in AUC for glucose to an OGTT) and plasma insulin concentrations (32% decrease in insulin AUC). However, on the day after the first exercise training bout, no effect on either glucose or insulin responses was seen compared with no exercise before training [22]. Likewise, we did not observe any change in glucose or insulin levels the day after an exercise bout of moderate intensity, whether continuous or accumulated.

Thus, 1 day of exercise at moderate intensity may not have an impact on glycemic control the following day in non-obese and type 2 diabetic individuals, but as little as 6 days of exercise training may alter these responses in individuals with type 2 diabetes [22]. The study of Rogers and our current study suggest that 1 day of acute exercise, whether accumulated or continuous, does not improve either glucose tolerance or insulin sensitivity in type 2 diabetes. In contrast, others have observed [13] both increased peripheral and splanchnic insulin sensitivity after a single exercise session in men with type 2 diabetes. Several differences exist, which may explain the discrepancies between our study and previous findings. First, a considerably higher exercise intensity (85% of Vo_{2peak}) was used by Devlin with the exercise duration continuing until muscular fatigue. Furthermore, these authors [13] used a hyperinsulinemic-euglycemic clamp, whereas we used an OGTT to examine glucose tolerance. Comparable to our study, Rogers et al [22] exercised their subjects at a moderate exercise intensity (68% Vo_{2peak}), also using an OGTT, and found no change in glucose control after 1 day of acute exercise.

Discrepancies in the findings may also be attributed to the duration from the last exercise bout and measurement of glucose and insulin levels. We studied our subjects 14 hours postexercise, which is slightly longer than that used by Devlin et al [13] (11 hours). Although the length of time between the exercise bout and the glucose load may seem small between these studies, the transient effect of exercise has been demonstrated previously in this population, with decreased glucose concentrations found 12 hours postexercise vs 72 hours postexercise [9]. These findings stress the importance of measuring the possibility of improved

glucose tolerance and/or insulin sensitivity within a short period after the last exercise session, rather than 2 to 4 days after the exercise session, which has been more common. This practice of testing 48 hours or more will tend to negate the possibility of finding positive effects associated with exercise. Although our study did not find such a benefit, it is possible the exercise intensity was much too low to elicit a positive effect.

An additional discrepancy between studies may be involve medications, particularly the use of oral hypoglycemic medications for those subjects with type 2 diabetes. For instance, Braun et al [17] discontinued oral hypoglycemic medications 7 days before study initiation, whereas our subjects continued using their medications as prescribed by their physicians, which may have negated the effect of a single day of exercise (whether accumulated or continuous). However, the use of hypoglycemic medications does not explain the lack of a condition effect in the non-obese control group in our study. It is possible that this group cannot become more sensitive to insulin given high baseline sensitivity, as estimated by the OGIS model. The insulin response to the no-exercise day (Fig. 3) would suggest the control group would not have much further room to improve, given the sharp increase in insulin at 30 minutes post-glucose load quickly followed by a sharp decrease to near 0 pmol/L at the end of the 4-hour OGTT. A single exercise session would appear not to alter this; however, the effect of multiple days of exercise is not known in this group.

Although other investigators have reported changes in glucose tolerance and insulin levels in individuals with type 2 diabetes not on their medications, we found that moderate aerobic exercise (60% VO_{2peak}) for 30 minutes, whether performed in a single continuous bout or accumulated from multiple sessions (ie, three 10-minute bouts), does not improve glucose tolerance or insulin sensitivity in either women with type 2 diabetes or in the non-obese control group compared with the no-exercise condition. Being in good glycemic control or on oral hypoglycemic agents may account for the lack of an exercise effect on glucose tolerance in this study.

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