Dose-Dependent Effects of Exercise and Diet on Insulin Sensitivity and Secretion

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ABSTRACT

DING, C., Y. C. CHOOI, Z. CHAN, J. LO, J. CHOO, B. T. K. DING, M. K.-S. LEOW, and F. MAGKOS. Dose-Dependent Effects of Exercise and Diet on Insulin Sensitivity and Secretion. *Med. Sci. Sports Exerc.*, Vol. 51, No. 10, pp. 2109–2116, 2019. **Purpose:** A single bout of aerobic exercise increases insulin sensitivity the next day. The effects of exercise on insulin secretion, the role of exercise-induced energy deficit, and possible dose–response relationships are not well understood. This study aimed to evaluate insulin sensitivity and insulin secretion after progressively greater negative energy balance induced by exercise or diet. **Methods:** Acute energy deficits (20% or 40% of weight maintenance needs) were induced by a single day of aerobic exercise (cycling at moderate intensity, $n = 13$) or dietary restriction ($n = 19$) in healthy men and women (age, 26 ± 2 yr; body mass index, 21.8 ± 0.5 kg·m^{-2}). Intravenous glucose tolerance tests in conjunction with minimal modeling were performed the next morning, and blood samples were collected for 3 h to measure glucose and insulin concentrations. **Results:** Insulin sensitivity increased linearly after exercise-induced energy deficits ($P = 0.007$) but did not change after equivalent diet-induced energy deficits ($P = 0.673$). Acute insulin response decreased after both exercise ($P < 0.001$) and dietary restriction ($P = 0.005$). The disposition index and glucose effectiveness were not affected by exercise ($P = 0.138$ and 0.808, respectively), but both decreased after 40% dietary restriction ($P = 0.048$ and 0.002, respectively). **Conclusions:** These results indicate that insulin sensitivity and insulin secretion are related to exercise energy expenditure, albeit in a different fashion (insulin sensitivity increases linearly, whereas insulin secretion drops to a nadir with a low exercise dose and does not decrease further). These changes cannot be replicated by equivalent energy deficits induced by dietary restriction, suggesting that exercise and diet have different effects on the mechanisms regulating glucose homeostasis. **Trial Registration:** ClinicalTrials.gov, NCT03264001. **Key Words:** INSULIN RESISTANCE, β-CELL FUNCTION, ENERGY EXPENDITURE, NEGATIVE ENERGY BALANCE

Regular exercise is associated with reduced risk for type 2 diabetes mellitus (1–3). The pathogenesis of diabetes involves the development of insulin resistance in combination with inadequate insulin secretion from pancreatic β cells (4). Exercise training, but also a single bout of aerobic exercise, increases skeletal muscle insulin sensitivity (5–7). However, the dose–response relationship between the amount of exercise and the enhancement of insulin action remains uncertain. We have previously reported that more than 900 kcal need to be expended during a single bout of moderate-intensity endurance exercise for an improvement in insulin sensitivity to manifest (8). This amount of exercise (equivalent to 60–90 min at moderate intensity per day) is well above public recommendations for physical activity (150 min·wk^{-1}) and likely unfeasible for most individuals, ~75% of whom do not even meet the current guidelines (9). However, interpretation of the results from our earlier study (8) is limited by its cross-sectional design, which is susceptible to the large interindividual variability in glucose and insulin responses to exercise (10), and the use of the Homeostasis Model Assessment (HOMA) index, which is merely a surrogate index of whole-body insulin resistance.

Contrary to the abundance of studies on exercise-induced changes in insulin sensitivity, comparatively less is known about the effects of exercise on pancreatic insulin secretion. Available studies report either no change or an increase in early phase insulin secretion in response to glucose after a single bout of endurance exercise (11), and no change (12,13) or a decrease (14,15) after exercise training. The reasons for these inconsistent findings could relate to different subject

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characteristics, changes in body weight and body composition with training, or different methods used to determine insulin secretion. No study to date has evaluated the dose–response relationship between the amount of exercise and pancreatic insulin secretion. Furthermore, aerobic exercise involves the expenditure of energy that invariably accompanies muscle contraction, so it is difficult to evaluate the contribution of exercise-induced energy deficit to the observed effects of exercise. Accordingly, this study aimed at evaluating insulin sensitivity and insulin secretion after a single day of progressively greater negative energy balance (20% and 40% of daily requirements for weight maintenance) induced by endurance exercise compared with equivalent energy deficits induced by dietary restriction. We hypothesized that exercise and diet would have the same effects on the mechanisms regulating glucose homeostasis when matched for negative energy balance.

MATERIALS AND METHODS

Subjects

A total of 32 subjects (22 women and 10 men) age 21–59 yr with a body mass index between 18 and 30 $kg \cdot m^{-2}$ participated in this study: 13 completed the exercise (EX) intervention and 19 completed the dietary restriction (DR) intervention. Initially, 15 subjects were randomized to each group by using an online research randomization tool and a two-subject block design, but after performing an interim analysis, we decided to recruit an additional 5 subjects in the diet group because the effect size turned out to be smaller than the one we had assumed to adequately power the study. As a result, a total of 15 subjects were recruited in the exercise group (2 dropped out and did not complete all trials; hence, 13 completers were analyzed; 10 women and 3 men), and a total of 20 subjects were recruited in the diet group (1 dropped out and did not complete all trials; hence, 19 completers were analyzed; 12 women and 7 men). Subjects had no history of glucose intolerance, hypertension, or dyslipidemia, and all but two had normal fasting blood glucose and HbA1c concentrations at screening (one subject in each group had fasting glucose concentrations between 102 and 104 $mg \cdot dL^{-1}$, with normal HbA1c). Subjects who were using medications known to affect metabolic function (including oral contraceptives and hormone replacement therapy), using tobacco products and consuming alcohol regularly, had evidence of significant organ system dysfunction or disease, and had recent weight loss or gain (≥5% over the past 6 months) were excluded from the study. Ethics approval was obtained from the Domain-Specific Review Board of the National Healthcare Group in Singapore (protocol no. 2016/00660), and all subjects provided their written informed consent before enrolment.

Experimental Design

Body composition and resting energy expenditure. After screening, subjects had their body composition measured by dual-energy x-ray absorptiometry and their resting metabolic rate (RMR) measured by indirect calorimetry, as previously described (16–19).

Metabolic testing. This was a parallel-group, crossover study, with subjects in each group performing three experimental trials in random order (separated by 5–10 d). For practical reasons, we did not consider the menstrual cycle phase when scheduling our female subjects because there is no evidence that this affects basal glucose metabolism and insulin sensitivity (20); nevertheless, we cannot rule out the possibility that the responses to DR and EX could vary. For all trials, subjects visited the laboratory in the morning (~8 AM on day 1), after having fasted overnight (Fig. 1). They were instructed to

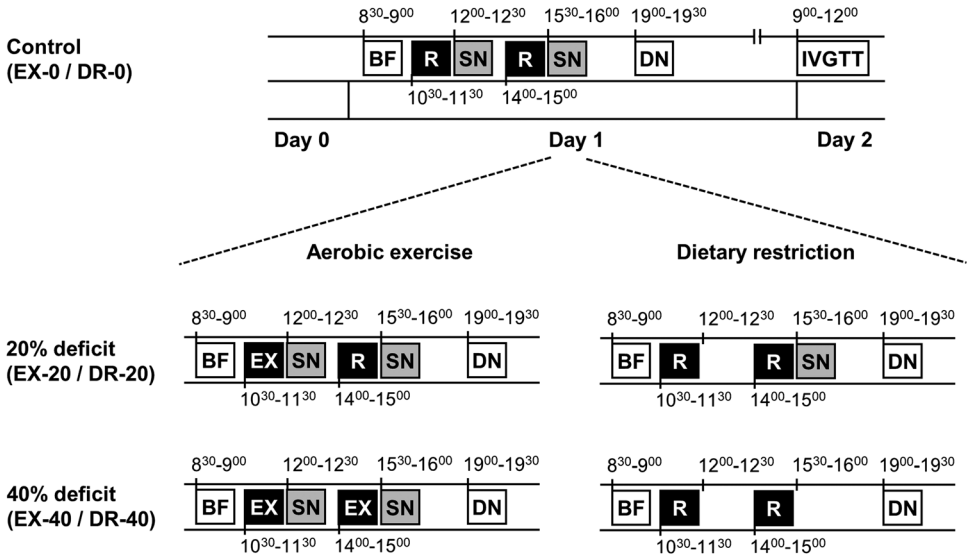

FIGURE 1—Experimental protocol. On day 1, subjects in both groups and all trials consumed an identical breakfast (BF) and dinner (DN), which provided 20% and 40% of the calories required for weight maintenance, respectively. Two snacks (SN), one in the morning and one in the afternoon, provided the remaining energy needed for weight maintenance (20% of calories each). In the EX group, subjects either rested (control) or performed one bout (20% deficit) or two bouts (40% deficit) of aerobic exercise (EX in the morning and afternoon of day 1), and ate all meals and snacks (isocaloric diet). In the DR group, subjects consumed both snacks (control), one snack (20% deficit), or no snacks (40% deficit), and rested (R) in the morning and afternoon of day 1, at approximately the same times of day as the exercise periods. After dinner, subjects fasted overnight and underwent an IVGTT the next morning.

abstain from alcohol and caffeine consumption on the previous day (day 0), and from performing any strenuous exercise on the preceding 3 d (to avoid potential delayed metabolic effects of exercise). Subjects recorded all food and drinks consumed on the day before they came to the laboratory (i.e., day 0) for their first metabolic testing visit and were instructed to replicate the same diet on the day preceding the remaining visits. On all occasions, vital signs (temperature, heart rate, and blood pressure) were obtained after 30 min of bed rest and before any testing began. During day 1, subjects remained in the laboratory and ate and rested or exercised according to the study protocol and trial (Fig. 1). They were discharged after eating dinner on day 1 and returned to the laboratory the next morning (~8 AM on day 2) to undergo an intravenous glucose tolerance test (IVGTT), after having fasted overnight (21,22). A glucose bolus (11.4 $g \cdot m^{-2}$ body surface area) was injected over 1 min, and 20 min later, a single bolus of insulin (0.03 $U \cdot kg^{-1}$ body weight) was infused over 5 min (from minute 20 to minute 25), whereas blood samples to measure glucose and insulin concentrations were collected for 3 h after glucose injection.

Diet and exercise interventions. Daily energy requirements for weight maintenance (i.e., isocaloric diet) were estimated for each subject by multiplying resting energy expenditure (RMR, measured at screening) by a factor of 1.4 (23). Two meals (breakfast, served at 8:30 AM, and dinner, served at 7 PM) were provided during each trial; the total energy content of those meals was equivalent to 60% of the total calculated daily energy requirements for weight maintenance (i.e., 20% at breakfast and 40% at dinner). These two meals were identical in all three trials (breakfast: turkey breast sandwich with soya milk; dinner: teriyaki chicken rice with mixed vegetables and peaches). Two snacks (tuna sandwich with orange juice) were given in the morning and afternoon to provide the additional energy required for weight maintenance (i.e., 20% at each snack, for a total of 40%). Subjects in the exercise group consumed an isocaloric diet on day 1 (i.e., both meals and both snacks in all trials) and either rested or performed aerobic exercise (two bouts, one in the morning and one in the afternoon; Fig. 1) to expend an amount of calories equivalent to 20% or 40% of their daily energy requirements for weight maintenance. Exercise was performed on a cycloergometer (Wattbike Trainer; Woodway, Rhein, Germany) at submaximal intensity, and the duration varied accordingly (range, 30–105 min) to expend the targeted amount of calories. Resistance varied so that the heart rate was within 60%–80% of the maximal heart rate, and cadence was maintained at 60–80 rpm. Gross energy expenditure (in kilocalories per minute) was calculated by using a prediction equation with age (in years), sex (1 for men, 0 for women), weight (in kilograms), and heart rate (in beats per minute) during exercise as inputs [total energy expenditure = $0.239 \times \text{sex} \times (-55.097 + 0.631 \times \text{heart rate} + 0.199 \times \text{weight} + 0.202 \times \text{age}) + 0.239 \times (1 - \text{sex}) \times (-20.402 + 0.447 \times \text{heart rate} - 0.126 \times \text{weight} + 0.07 \times \text{age})$] (24), and net energy expenditure was calculated by subtracting RMR for the duration of the bout. To minimize subject discomfort, we decided not to use indirect calorimetry during exercise. This may have added some inaccuracy in our estimates of total energy expenditure, for example, the contribution from excess postexercise oxygen consumption (~7% of the net total oxygen cost of a submaximal exercise bout) (25), but this is more relevant for the between-group comparisons between exercise and diet rather than the within-group comparison between exercise trials. Subjects in the diet group rested during the morning and afternoon of day 1 (all trials) and consumed either an isocaloric diet (control) or a progressively energy-deficient diet by withholding one (20% dietary restriction) or both (40% dietary restriction) snacks. All meals were prepared in the metabolic kitchen of the Clinical Nutrition Research Centre. Each meal or snack contained 55% of total energy as carbohydrate, 27% as fat, and 18% as protein, so the relative composition of the diet was the same in both groups and all trials. This design allowed for inducing progressively greater energy deficits (equal to 20% and 40%) by increasing exercise energy expenditure (EX-0/EX-20/EX-40) or restricting dietary energy intake (DR-0/DR-20/DR-40) at approximately the same time of the day, while keeping the last meal and the duration of fasting before metabolic testing the same (Fig. 1).

Sample Analyses

Plasma glucose concentrations were determined on an automated glucose analyzer (YSI 2300 Stat Plus; YSI Life Sciences, Yellow Spring, OH), and plasma insulin concentrations were determined by using electrochemiluminescence technology (Roche/Hitachi cobas e411 immunochemistry analyzer; Roche Diagnostics, Indianapolis, IN).

Calculations

Whole-body insulin sensitivity (Si), the acute insulin response to glucose (AIR), the disposition index (DI; which provides an assessment of the appropriateness of insulin secretion in relationship to peripheral insulin sensitivity; i.e., β-cell function), and glucose effectiveness (Sg; which provides a metric of the ability of glucose itself to promote its own uptake) were determined by minimal modeling analysis of the glucose and insulin concentration data during the 3 h of the IVGTT with the MinMod Millennium software (21,26). The minimal model is the simplest model that can account for the observed relationship between the glucose-insulin data after an IVGTT and embodies two key concepts of glucoregulation: (i) once glucose is elevated by injection, it returns to baseline levels not only because of the action of insulin on peripheral glucose uptake but also because of the effect of glucose itself to normalize its own concentration, and (ii) the effect of insulin on glucose disappearance exhibits a time delay. These concepts are described in two equations: one that relates glucose disappearance to glucose and insulin levels, and a second that describes the kinetics of insulin movement (27).

TABLE 1. Energy intake and expenditure during progressively greater negative energy balance in the EX and DR groups.

	EX (n = 13)			DR (n = 19)		
	EX-0	EX-20	EX-40	DR-0	DR-20	DR-40
Dietary energy intake, kcal	1688 ± 66	1688 ± 66	1688 ± 66	1793 ± 96	1434 ± 76*	1076 ± 57*,**
Carbohydrate, g·d^{-1}	232 ± 9	232 ± 9	232 ± 9	247 ± 13	197 ± 11*	148 ± 8*,**
Protein, g·d^{-1}	76 ± 3	76 ± 3	76 ± 3	81 ± 4	65 ± 3*	48 ± 3*,**
Fat, g·d^{-1}	51 ± 2	51 ± 2	51 ± 2	54 ± 3	43 ± 2*	32 ± 2*,**
Calorie restriction, kcal	0	0	0	0	359 ± 19*	717 ± 38*,**
Exercise energy expenditure, net, kcal	0	323 ± 12*	673 ± 28*,**	0	0	0
Duration, min	0	36 ± 2*	70 ± 4*,**	—	—	—
Heart rate, bpm	0	141 ± 4*	147 ± 3*,**	—	—	—
Intensity, % of maximal heart rate	0	73 ± 2*	76 ± 2*,**	—	—	—
Energy balance, %	0	−19 ± 0*	−40 ± 0*,**	0	−20 ± 0*	−40 ± 0*,**

Data are mean ± SEM and were collected on day 1.
*Value is significantly different from corresponding value in the control trial of zero energy balance (EX-0/DR-0; $P \leq 0.05$).
**Value is significantly different from corresponding value in the trial of 20% negative energy balance (EX-20/DR-20; $P \leq 0.05$).

Statistical Analysis

Differences between the two groups at baseline were evaluated by using the Student's unpaired t-test. The primary goal of our study was to determine the metabolic effects of progressively increasing negative energy balance induced by endurance exercise and dietary restriction. This was accomplished by using ANOVA for repeated measures within each subject group. Statistically significant models were followed by (i) simple contrasts to compare each level of energy deficit against the control trial of zero energy balance and (ii) trend analysis to describe the pattern of change with progressively increasing negative energy balance. We computed the P value for the linear and quadratic components of the line describing the change from the control trial to the 20% and 40% energy deficit trials (the line defined by $v = 3$ data points can be described by an equation with maximum of $v - 1 = 2$ components). A significant linear component without a significant quadratic component indicates that the change (control → 20% → 40%) is overall linear; i.e., $y = \alpha x + \beta$. When both the linear and quadratic components are significant, this indicates that the change (control → 20% → 40%) has a leveling off or a bend, either upward or downward; i.e., $y = \alpha x^2 + \beta x + \gamma$. Statistical significance was accepted at $P \leq 0.05$. Results are means with SE. Statistical analysis was performed with SPSS version 23 (IBM SPSS, Chicago, IL).

RESULTS

Subject characteristics. There were no differences between the exercise and diet groups in age (25.9 ± 2.6 and 26.4 ± 2.2 yr, respectively; $P = 0.89$), sex ($P = 0.41$), body mass index (20.9 ± 0.5 and 22.5 ± 0.8 kg·m^{-2}, respectively; $P = 0.10$), percent body fat (32% ± 1% and 30% ± 1%, respectively; $P = 0.24$), and RMR (1206 ± 47 and 1281 ± 68 kcal·d^{-1}, respectively; $P = 0.38$).

Energy intake and expenditure (day 1). The exercise and diet interventions were successful in inducing energy deficits equal to 20% and 40% of daily energy needs (Table 1). By design, subjects in the exercise group exercised progressively more in the 20% and 40% trials (by ~35 and ~70 min, respectively, compared with the control trial), and subjects in the diet group ate progressively less in the 20% and 40% trials (by ~350 and ~700 kcal, respectively, compared with the control trial; Table 1).

Metabolic function (day 2). Negative energy balance induced by exercise or diet did not significantly affect resting blood pressure and heart rate, and fasting plasma glucose and insulin concentrations (Table 2). Plasma glucose and insulin concentrations during the IVGTT for the three trials in each group are shown in Figure 2. AIR decreased after both exercise ($P < 0.001$) and diet ($P = 0.005$) interventions, albeit in a different fashion; AIR decreased to a nadir after relatively little exercise but decreased linearly after dietary restriction (Fig. 3A). Si increased after exercise ($P = 0.007$) in a linear fashion but did not change after diet ($P = 0.673$; Fig. 3B). Neither DI nor Sg was affected by exercise ($P = 0.138$ and 0.808, respectively), whereas both decreased after 40% energy deficit induced by dietary restriction ($P = 0.048$ and 0.002, respectively; Fig. 3C and D).

DISCUSSION

The exercise-induced improvement of peripheral insulin sensitivity (6), along with favorable changes in body weight and body composition, is often cited as the key mediating factor for the protective effects of regular exercise against the

TABLE 2. Effects of negative energy balance induced by EX and DR on resting blood pressure, heart rate, and fasting plasma glucose and insulin concentrations.

	EX (n = 13)			DR (n = 19)		
	EX-0	EX-20	EX-40	DR-0	DR-20	DR-40
Systolic blood pressure, mm Hg	109 ± 4	112 ± 4	106 ± 3	115 ± 2	113 ± 3	114 ± 3
Diastolic blood pressure, mm Hg	71 ± 3	70 ± 2	70 ± 2	72 ± 1	72 ± 2	71 ± 1
Heart rate, bpm	73 ± 3	75 ± 3	73 ± 3	74 ± 2	76 ± 3	77 ± 2
Fasting plasma glucose, mg·dL^{-1}	88 ± 2	87 ± 2	90 ± 2	90 ± 2	89 ± 2	88 ± 2
Fasting plasma insulin, mU·L^{-1}	8 ± 1	7 ± 1	7 ± 1	8 ± 1	8 ± 1	7 ± 1

Data are mean ± SEM and were collected on day 2.

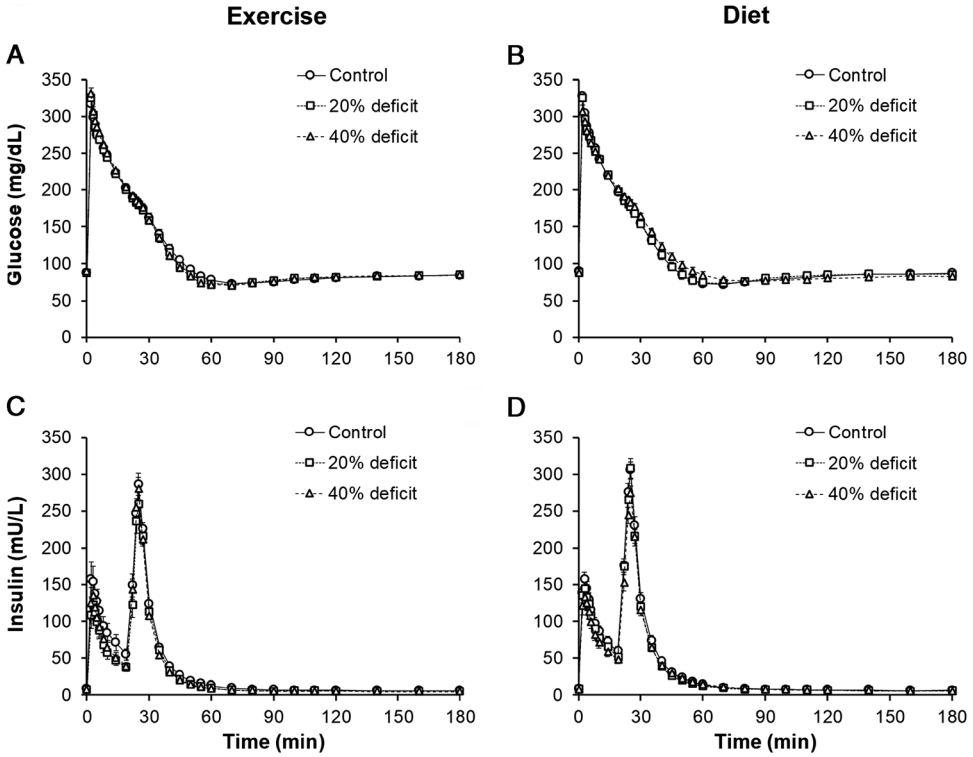

FIGURE 2—Effects of negative energy balance induced by exercise and diet on plasma glucose (A and B, respectively) and insulin (C and D, respectively) concentrations during an IVGTT. Data are mean ± SEM and were collected on day 2 for n = 13 (exercise group) and n = 19 (diet group).

development of type 2 diabetes (2,3). Interestingly, however, the greater insulin sensitivity of trained subjects compared with sedentary controls is almost completely abolished after just a few days of detraining (60 h without exercise), before any changes in body composition and physical fitness occur (28). This suggests that much of the enhancement in insulin sensitivity associated with chronic exercise is the result of the last bout of exercise (i.e., an acute effect), although adaptive mechanisms after exercise training may contribute to an augmented response (5,7). In fact, insulin action increases after just a single bout of exercise for at least 48 h into recovery, predominantly because of greater insulin-mediated glucose uptake in the previously exercised muscles (7). Despite this (and other) well-established beneficial health effects of regular exercise, fewer than one in four adults meet the current public recommendations for physical activity (150 min of moderate-intensity exercise per week) (9). It is therefore important to characterize the dose–response relationship between endurance exercise and the mechanisms regulating glucose homeostasis, i.e., insulin sensitivity and insulin secretion, to facilitate physical activity recommendations and exercise prescription.

Contrary to our previous study in which we found that the acute exercise-induced improvement in whole-body insulin resistance, determined by the HOMA index, was curvilinearly related to exercise energy expenditure (8), here we found that insulin sensitivity, assessed by an IVGTT and minimal modeling the day after exercise, increases linearly with exercise energy expenditure. Our 20% and 40% energy deficits corresponded to approximately 350 and 700 kcal, respectively, both of which are below the apparent threshold (~900 kcal) we observed earlier for an improvement in insulin action to manifest (8). The inability of the HOMA to acutely capture dynamic changes in insulin action (29), the large interindividual variability in the HOMA response to exercise at energy expenditures between 300 and 600 kcal (8), and the less strict dietary control might have confounded our earlier observations at lower exercise-induced energy deficits. In this study, we had the same subjects perform three trials of progressively greater negative energy balance, in random order, while eating the same exact diet, and used minimal modeling of the IVGTT data to evaluate insulin sensitivity, and we found that Si increases linearly with exercise energy expenditure. Contrary to our observations after exercise and our hypothesis, we found no changes in insulin sensitivity after equivalent energy deficits induced by dietary restriction. Although acute dietary manipulations of energy balance may occasionally affect fasting plasma glucose and insulin concentrations, and therefore the HOMA index (30), our results suggest that the negative energy balance accompanying exercise is not the primary factor responsible for the improvement in insulin action. Previous studies that replenished the calories expended during exercise in the post-exercise period yielded inconsistent results. In one study where 100 g of carbohydrate was consumed within 3 h after a bout of glycogen-depleting endurance exercise, the insulin-mediated increase in muscle glucose uptake the

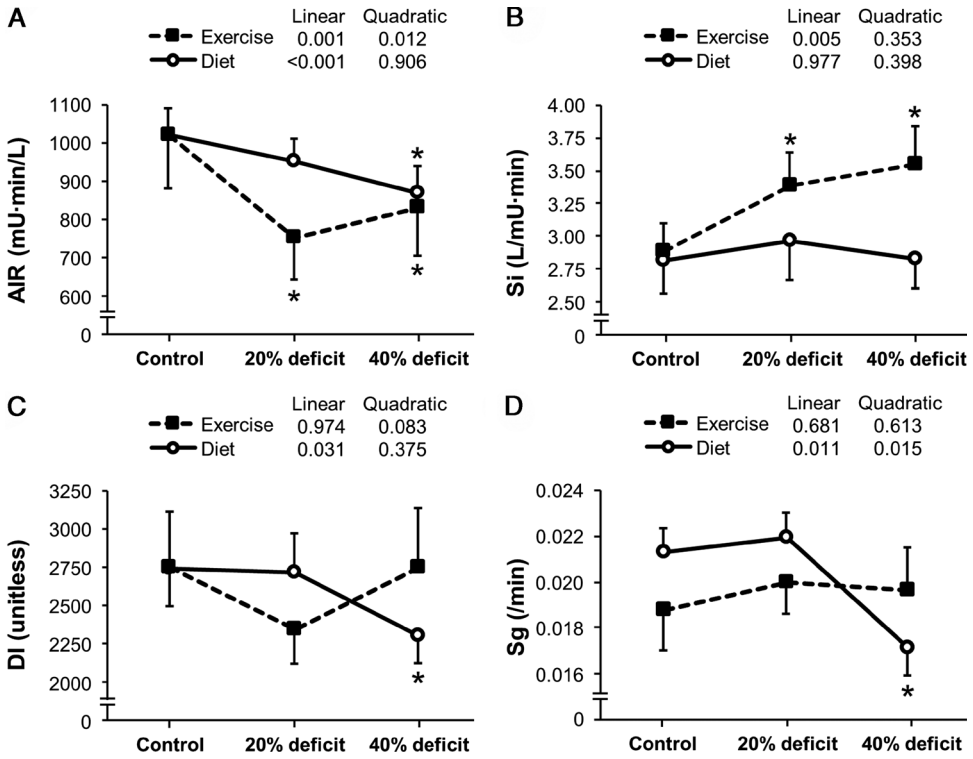

FIGURE 3—Effects of negative energy balance induced by exercise and diet on the AIR (A), Si (B), DI (C), and Sg (D). Data are mean ± SEM and were collected on day 2 for $n = 13$ (exercise group) and $n = 19$ (diet group). *Value is significantly different from corresponding value in the control trial of zero energy balance ($P \leq 0.05$).

next day was almost completely abolished (31). On the contrary, administration of surplus calories from fat (165 g orally or 110 g intravenously) after a single bout of aerobic exercise did not impair the exercise-induced increase in whole-body insulin sensitivity the next morning (32,33). These observations, together with our findings, suggest that changes in energy balance induced by endurance exercise are not critical for the postexercise improvement in insulin sensitivity, but changes in nutrient balance—and particularly fat and carbohydrate—may be important, possibly by modulating the rates of muscle glycogen replenishment (34).

Very few studies have evaluated insulin secretion after a single bout of aerobic exercise, and most have conducted their measurements during the first 1–2 h after exercise cessation. Nikkila et al. (35) used a radioactive insulin tracer infusion and concluded that exercise leads to a mild increase in pancreatic insulin secretion rate. Malin et al. (11) recently reported that exercise at high intensity increases early phase insulin secretion—evaluated by deconvolution of C-peptide data during a standard oral glucose tolerance test—compared with a resting trial but also compared with an isocaloric bout of exercise at low intensity. Similarly, the effects of chronic exercise training have been inconsistent, with some investigators reporting no change in insulin secretion (12,13) and others reporting a decrease (14,15). We used minimal modeling of IVGTT data the day after exercise and found that aerobic exercise decreased insulin secretion (i.e., AIR), and the magnitude of the decrease was the same for the two exercise-induced energy deficits (20% and 40%). Unfortunately, our methodology cannot tease out the contribution from changes in insulin clearance to the observed changes in insulin response. For instance, it has been shown that a single bout of prolonged exercise increases insulin clearance for up to 2 d after exercise cessation, in addition to decreasing insulin secretion; hence, both mechanisms likely contribute to the lower postexercise insulin response (36). Dietary restriction also decreased AIR, but in a different manner than exercise; reductions after 20% diet-induced energy deficit were smaller in magnitude than those after 40% energy deficit. This finding is in agreement with an earlier study in obese subjects with normal glucose tolerance, in whom 3–6 d of fasting led to a robust decrease in insulin secretory capacity, which coincided with the development of insulin resistance (37). These results suggest that, in the short term (i.e., before any major changes in body weight and body composition occur), greater and more prolonged diet-induced energy deficits decrease the ability of the pancreas to secrete insulin, at least temporarily, which may eventually compromise insulin-mediated glucose disposal. This is consistent with the reduction in the DI we observed after the greater diet-induced energy deficit. Furthermore, glucose disposal under these conditions will be further impaired by the lower glucose effectiveness. All these changes are likely the result of a coordinated adaptive response to excessive dietary restriction to conserve glucose for obligatory glucose-consuming organs (e.g., brain). This is clearly a very different response from the increase in glucose disposal after acute

energy deficits induced by aerobic exercise. Our study cannot delineate the mechanisms for the exercise-induced decrease in AIR. Given that exercise did not affect the DI, it is reasonable to assume that the reduction in AIR is likely the result of the increase in peripheral insulin action. After exercise, less insulin is required to maintain the same glucose homeostasis, hence the reduced AIR. Nevertheless, we cannot exclude the possibility of direct effects of exercise on pancreatic islets independently of the glucose stimulus, perhaps via neural (e.g., cholinergic) and hormonal signals (38).

The strengths of our study include the use of carefully controlled exercise and diet interventions, matched for the timing and the magnitude of energy deficits. On the other hand, our study has a number of limitations. First, we only tested the effects of moderate-intensity continuous exercise on the mechanisms regulating glucose homeostasis. It is not known whether other forms of exercise (e.g., high-intensity interval or resistance exercise) used to generate equal energy deficits will have the same effects or not. Furthermore, our methodology was not able to distinguish between the ability of insulin to stimulate glucose uptake (i.e., skeletal muscle insulin sensitivity) and its ability to suppress glucose production (i.e., hepatic insulin sensitivity). Also, our study involved single-day energy deficits induced by aerobic exercise and dietary restriction, and thus, we cannot extrapolate our results to the long term and make inferences about the long-term comparative therapeutic efficacy of exercise and diet. In addition, the IVGTT does not allow for evaluating the contribution from gut-derived hormones, such as glucagon-like peptide 1, to insulin secretion under the more physiological scenario of oral glucose ingestion. There is some evidence that a single bout of exercise increases (39), whereas a single day of dietary restriction does not affect (40), glucagon-like peptide 1 responses, so it is possible that our results might have been different had we chosen an oral test to evaluate insulin secretion. We opted to use the IVGTT to measure insulin sensitivity, insulin secretion, glucose effectiveness, and β-cell function with a single test and on a single occasion. Using an oral test to assess the incretin effect would require repeating the whole trial on a different day so that insulin sensitivity could also be assessed by a different test (e.g., IVGTT or euglycemic–hyperinsulinemic clamp) (16–19), hence doubling the number of trials each subject would have to undergo. Last but not least, the amount of exercise we tested (particularly the 40% negative energy balance trial, which was equivalent to ~700 kcal) may not be practical or even feasible for most individuals in real life. In fact, we only studied healthy individuals so we cannot extrapolate our results to clinical populations, such as patients with type 2 diabetes, many of whom are resistant to the beneficial effects of exercise (41).

In summary, we found that acute negative energy balance induced by aerobic exercise has a dose-dependent beneficial effect on peripheral insulin sensitivity in subjects with normal glucose tolerance and, accordingly, diminishes the need for insulin and thereby decreases pancreatic insulin secretion. The responses to exercise are different from the changes in insulin sensitivity and insulin secretion after equivalent energy deficits induced by dietary restriction, suggesting that negative energy balance *per se* is not the mediating factor. Future studies should focus on understanding the mechanisms by which progressive exercise and dietary restriction affect the mechanisms regulating glucose homeostasis.

The authors would like to thank the study subjects for their participation. The results of the study are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation. The results of the present study do not constitute endorsement by the American College of Sports Medicine. Award BMSI/16-07803C-R20H (F. M.) from Singapore Institute for Clinical Sciences, Agency for Science, Technology and Research (A*STAR), Singapore. The authors have no conflicts of interest relevant to the content of this article.

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