Inactivity Causes Resistance to Improvements in Metabolism After Exercise

Edward F. Coyle, Heath M. Burton, and Remzi Satiroglu

Human Performance Laboratory, Department of Kinesiology and Health Education, The University of Texas at Austin, Austin, TX

COYLE, E.F., H.M. BURTON, and R. SATIROGLU. Inactivity causes resistance to improvements in metabolism after exercise. *Exerc. Sport Sci. Rev.*, Vol. 50, No. 2, pp. 81–88, 2022. *Prolonged sitting prevents a 1-h bout of running from improving fat oxidation and reducing plasma triglycerides. This "exercise resistance" can be prevented by taking 8500 steps·d^{-1} or by interrupting 8 h of sitting with hourly cycle sprints. We hypothesize that there is an interplay between background physical activity (e.g.*, steps·d^{-1}) and the exercise stimuli in regulating some acute and chronic adaptations to exercise. **Key Words:** obesity, insulin resistance, inactivity, lipid oxidation, exercise, training

Key Points

- Prolonged sitting throughout the day prevents a subsequent bout of exercise from causing the normal postprandial increase in fat oxidation and lowering of plasma triglyceride concentration (*i.e.*, "exercise resistance").
- Exercise resistance can be prevented by taking 8500 steps·d^{-1} or by interrupting 8 h of sitting with several hourly high-power cycle sprints of 4-s duration.
- A background of low daily steps during short-term aerobic training significantly blunts some classic metabolic adaptations, indicating that exercise resistance extends beyond just fat metabolism.
- We hypothesize that there is an interplay between background physical activity (*e.g.*, steps per day) and the exercise stimuli in regulating some acute and chronic adaptations to exercise and training.
- Therefore, if the goal is to maintain a high rate of fat oxidation, even in people who meet the recommended guidelines for exercise, it is necessary to be active when not exercising. The level of background physical activity seems important in developing exercise and physical activity guidelines.

INTRODUCTION

Physical inactivity is becoming increasingly more prevalent as fewer people walk for transportation or perform manual labor and more people spend most of their waking hours sitting or standing, often behind a computer screen (1,2). In fact, 77% of American adults and adolescents are considered to be physically "inactive," and they fail to meet the recommendations of the Physical Activity Guidelines of 150–300 min·wk^{-1} of moderate-intensity aerobic exercise or 75 min·wk^{-1} of vigorous-intensity exercise and 2 d·wk^{-1} performing strength training (2–4). Because inactivity is associated with a significantly greater risk of cardiovascular disease, diabetes, and cancer (5), it is imperative that we discover various types of exercise and strategies that can ward off the ailments caused by inactivity (3,4). Physical inactivity is a global pandemic estimated to result in 5 million deaths per year (6). The health care costs of inactivity are staggering and estimated to be 53.8 billion per year worldwide (6).

The first issue to appreciate is that inactivity causes unique detrimental physiological effects and, as such, is more than simply the lack of exercise. It is our premise that inactivity before a 1-h bout of exercise produces unique molecular signals that stall metabolism, with one of its most obvious effects being a reduction in fat oxidation when fasted and during the 6-h period after ingesting a high-fat meal (Fig. 1). Furthermore, elevated postprandial plasma triglyceride concentration (PPTG) after acute inactivity seems related to reduced triglyceride uptake by muscle (Fig. 1) that has been associated with reduced muscle lipoprotein lipase (mLPL) activity (7–11). As early as 1979, atherosclerosis, a major risk factor for cardiovascular disease, was described as a "postprandial phenomenon" driven by lipid accumulation in arteries because of prolonged elevation of plasma triglycerides after meals (12). The discipline of "inactivity physiology" has been pioneered by the works of Frank Booth (13) and Marc Hamilton (7) and others (14). The profound cardiovascular effects and exercise responses to 21 d of bed rest inactivity were first reported in 1968, with a 30-year follow-up study concluding that bed rest inactivity was comparable to three decades of aging (15).

HYPOTHESIS

"*Physical inactivity causes resistance to some metabolic benefits of acute and chronic aerobic exercise*" (Fig. 1).

Address for correspondence: Edward F. Coyle, Ph.D., Department of Kinesiology & Health Education, The University of Texas at Austin, 2109 San Jacinto Blvd, Austin, TX 78712 (E-mail: coyle@austin.utexas.edu).

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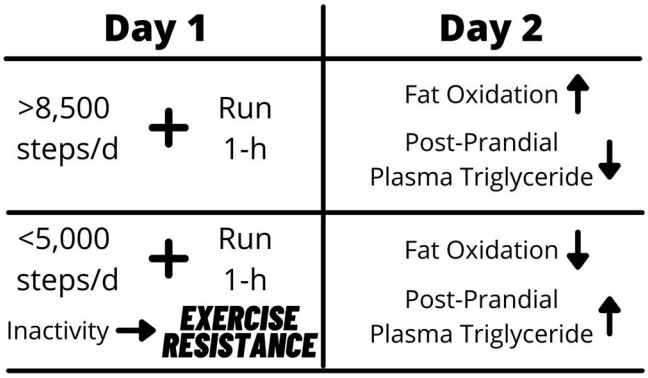

Figure 1. Displayed is the experimental model used to detect exercise resistance. Walking more than 8500 steps·d^{-1} and performing a 1-h run on day 1 stimulates an increase in fat oxidation and a lowering of plasma triglyceride concentration (PPTG) on day 2. This is a "normal" and healthy response. However, if walking less than 5000 steps·d^{-1} on day 1, a 1-h run fails to stimulate an increase in fat oxidation or the lowering of PPTG on day 2. When inactive (<5000 steps·d^{-1}), it seems that a 1-h run has no beneficial effect on fat metabolism or that the body is "resistant" to the normally beneficial effects of "exercise" (*i.e.*, exercise resistance).

It is our hypothesis that inactivity (*e.g.*, <5000 steps·d^{-1}) in the days before acute exercise prevents the bout of exercise (*e.g.*, 1 h of running at 65% VO_{2max}; Fig. 1) from displaying the "healthy" response after exercise, which is increasing fat oxidation and lowering PPTG concentration the next morning. This attenuation of the "healthy" responses to exercise is a phenomenon termed "exercise resistance" (Fig. 1).

Hamilton *et al.* (7) have made compelling arguments that inactivity and exercise have major acute effects on mLPL, although potentially through different mechanisms (10). Impaired whole-body fat oxidation seems to be related to reduced clearance of plasma triglyceride in the postprandial state and results in an elevation of PPTG (16). We have used these postprandial measures as reflections of healthy (*i.e.*, high fat oxidation and low plasma triglyceride (TG) concentration) and unhealthy responses (*i.e.*, lower fat oxidation and high plasma TG concentration) after a high fat meal. An advantage of this model (Fig. 1) is that the metabolic effects of inactivity or exercise can be manifest within 1 d or even hours, which also coincides with the time course of mLPL turnover (17). For example lipoprotein lipase (LPL) mRNA peaks 4 h after exercise, and subsequent protein levels of mLPL protein are increased by 8 h after exercise and returned to basal levels 20 h after exercise (17). Studies have shown that prolonged inactivity decreases the amount of heparin releasable LPL protein and may reduce LPL's activity by up to 90% (7–11). Our model establishes a level of background physical activity from the number of steps per day taken over 2–4 d (Fig. 1). The participants then run for 1 h at a moderate intensity (63%–65% VO_{2max}) in the evening so as to establish a robust aerobic signal for potential acute adaptation. Afterward, the next morning, the PPTG and fat oxidation responses are measured over a 6-h postprandial period. It is our hypothesis that inactivity in the 1–4 d before exercise prevents the 1-h bout of exercise from increasing fat oxidation and lowering PPTG (*i.e.*, causing exercise resistance; Fig. 1).

Our First Observations of Exercise Resistance

Holloszy *et al.* (18) first reported in 1964 that plasma TG is reduced the morning after exercise. This topic has been reviewed in a meta-analysis (19). General observations are that more intense interval exercise has a larger effect on lowering PPTG and that exercise in women has a much larger effect on PPTG than it does in men. In 2013, we verified the healthy responses by demonstrating that after high-intensity exercise compared with moderate-intensity exercise, there is a more robust lowering of PPTG and increased fat oxidation in physically active people (20). In terms of diet, low carbohydrate composition of a postexercise meal reduced PPTG and increased whole-body fat oxidation, independent of energy content (21), suggesting a fate of at least a part of the plasma triglyceride cleared from the circulation is direct oxidation. The issue of whether low background physical activity is detrimental was not addressed in the meta-analysis or in early studies (19), and it was typical for the subjects to be physically active with a background level of ~7800 steps·d^{-1} (20), which discussed below is likely sufficient to prevent exercise resistance.

Interestingly, in 2016, we reported that prolonged sitting over 2–4 d and taking only ~1700 steps·d^{-1} prevented an acute bout of running (1 h at 65% VO_{2max}) from improving (lowering) the next morning's PPTG response to a high-fat meal and also failed to increase postprandial fat oxidation (22) (Fig. 2A). This is exercise resistance because the usually robust effect of acute exercise (1-h run) for improving the next morning's fasting and

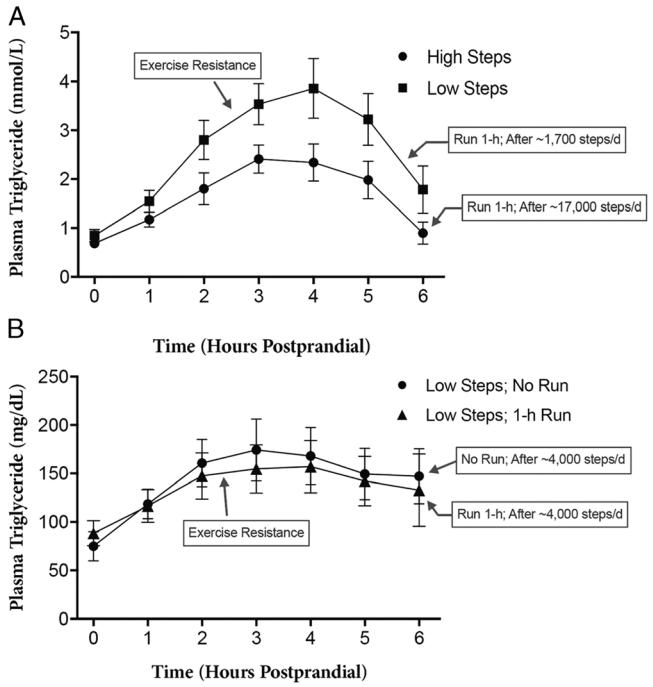

Figure 2. Plasma triglyceride response during the 6-h postprandial period in (A), when subjects ran for 1 h the evening after either taking ~1700 steps (LS) or ~17,000 steps (HS) the day before. The 1-h run was effective in lowering the postprandial triglyceride response when steps were high but not when steps were low (*i.e.*, exercise resistance) (22). In (B), the steps were low (~4000 steps·d^{-1}) and sitting was high in both trials, and the 1-h run failed to lower the postprandial triglyceride response (*i.e.*, exercise resistance). [Panel A adapted from Kim IY, Park S, Chou TH, Trombold JR, Coyle EF. Prolonged sitting negatively affects the postprandial plasma triglyceride-lowering effect of acute exercise. Am. J. Physiol. Endocrinol. Metab. 2016; 311(5):E891-E898. Copyright © The American Physiological Society. Used with permission.] [Panel B adapted from Akins JD, Crawford CK, Burton HM, Wolfe AS, Vardarli E, Coyle EF. Inactivity induces resistance to the metabolic benefits following acute exercise. J. Appl. Physiol. 2019; 126(4):1088-1094. Copyright © The American Physiological Society. Used with permission.]

postprandial fat metabolism when taking 1700 steps·d^{-1} was significantly impaired (22) (Fig. 2A). We discuss below that 1700 steps·d^{-1} seems to prevent improvement in fat metabolism even though subjects also ran for 1 h at 65% $\dot{V}O_{2max}$ in the evening, which is a large amount of moderate-intensity exercise, had a mixed dinner, and returned to the laboratory the next morning and had fat oxidation measured during a 6-h postprandial test of the increases in plasma triglyceride concentration (PPTG) (Fig. 1). When the subjects were inactive, largely sitting, and taking few steps, they displayed a 30% elevation in PPTG despite having run 1 h the evening before (Fig. 2A). Furthermore, their rate of fat oxidation was only approximately one half of that when they were taking a large number of steps. Our measures of fat metabolism agree with epidemiological studies reporting adverse effects of prolonged sitting on cardiovascular health and all-cause mortality, independent of participation in exercise or physical activity (23). Therefore, meeting exercise guidelines but being inactive throughout the day may not reduce all-cause mortality or exercise resistance. We use the PPTG responses and fat oxidation as an acute marker of cardiometabolic health, as it provides a model to identify the amount and type of background physical activity needed to overcome exercise resistance and maintain healthy fat metabolism (Fig. 1).

A key question is "How does a low background physical activity (*i.e.*, low steps) during the waking hours impair the normally healthy adaptations to acute exercise regarding 'fat metabolism'?" We have eliminated the possibility that inactivity stalls fat metabolism because of a positive energy balance by demonstrating that if caloric intake is reduced to match the reduction in steps, that exercise resistance is not attenuated (21). The significant association between a reduced fat oxidation and elevated PPTG could indicate that inactivity impairs a step in fat metabolism that normally leads to oxidation (20). The most likely candidate for the stalling of fat metabolism with inactivity is muscle LPL activity (10).

A Second Indication of Exercise Resistance

To verify our previous report of exercise resistance and that prolonged inactivity prevents a bout of exercise from up-regulating fat metabolism, we directly compared the PPTG responses when subjects remained inactive by taking 3500–4000 steps·d^{-1} of background activity. They either did no exercise or ran for 1 h at ~62% $\dot{V}O_{2max}$ the evening before measurements (24). The addition of the 1-h bout of running when having a low step count had absolutely no effect on improving the next morning's PPTG response or fat oxidation (Fig. 2B). This is another example of exercise resistance. Typically, as discussed, a 1-h bout of exercise results in subsequent robust improvement in PPTG and fat oxidation (25) in subjects who are active and presumably above the threshold number of steps for maintaining a healthy fat metabolism. However, it seems that if activity throughout the day is low (*e.g.*, <4000 steps in this study), even a 1-h run does not improve fat metabolism (24). Thus, Figure 2A demonstrates that a 1-h run is not effective for improving fat metabolism when the background steps per day are low (*i.e.*, 1700 steps·d^{-1}), and Figure 2B demonstrates that when the background steps per day are low (*i.e.*, ~4000 steps·d^{-1}), a 1-h run does not improve fat metabolism. These observations imply that when developing recommendations of the amount of exercise needed to improve health, consideration also should be given to the amount of exercise needed to prevent exercise resistance; otherwise, the full benefits of the exercise will not be realized.

Several epidemiological studies have concluded that prolonged sitting is a significant risk factor for cardiovascular disease and mortality even in people who meet the recommended level of physical activity and exercise (*i.e.*, 150 min·wk^{-1} of moderate-intensity or 75 min·wk^{-1} of vigorous-intensity physical activity) (26–28). Ekelund *et al.* (23) hypothesized that ~60–75 min·d^{-1} of moderate-intensity physical activity might be needed to offset the cardiovascular disease risk and increased mortality associated with prolonged sitting. The observation of Akins *et al.* (24) that 60 min of exercise at ~63% $\dot{V}O_{2max}$ on a single day did not offset the effects of 13.5 h·d^{-1} of sitting and ~4000 steps·d^{-1} in terms of fat metabolism, represents a preliminary test of the hypothesis that 60 min·d^{-1} of moderate-intensity exercise as derived by Ekelund *et al.* (23) may not be able to maintain a healthy fat metabolism. In Akins *et al.* (24), the end points of acute fat metabolic responses is different from cardiovascular disease and mortality as measured by Ekelund *et al.* (23). However, both the conclusions of Ekelund *et al.* (23) and that of Akins *et al.* (24) indicate that, in people who sit for prolonged periods and take <4000 steps·d^{-1}, the amount of exercise needed to maintain a healthy fat metabolism is large or possibly the intensity needs to be quite high (see below). The 1-h bout of running at 63% $\dot{V}O_{2max}$ was not effective despite amounting to 7.7 km, ~8000–10,000 steps, and an average exercising heart rate of 158 beats·min^{-1} in the subjects of Akin's *et al.* (24). This intensity and distance of exercise, although not exhausting, probably represent the upper limit of what people might choose to do voluntarily. The implication is that, in practice, prolonged exercise does not counteract prolonged sitting, at least when the exercise is done late in the day after prolonged sitting (24).

Accordingly, our observations of a lack of benefit from 1 h of running are probably not due to an inadequate exercise stimulus but probably due to maintained exercise resistance. This suggests that some effect from a day's inactivity carries over at least through the next day with profound effects on reducing fat oxidation. It seems that the negative effects of inactivity throughout 1 d (*e.g.*, <4000 steps·d^{-1}) is more potent than even 1 h of moderate-intensity exercise in the evening of the same day in terms of regulating fat oxidation and the postprandial increase in plasma triglyceride concentration on the following day. Therefore, if the goal is to maintain a high rate of fat oxidation, even in people who meet the recommended guidelines for exercise, it is advisable to be active when not exercising. Interestingly, the amount of physical activity of marathon runners, outside of their daily training, is very low (29), and it would be interesting to see if they experience exercise resistance. It also is possible that greater amounts of exercise than we have studied (*e.g.*, >60 min at 65% $\dot{V}O_{2max}$) can counteract the effects of inactivity.

Is Standing Different Than Sitting?

Rather than sitting for prolonged periods throughout the day, many people have resorted to standing. We compared 1 d of sitting (14.4 ± 0.3 h) to 1 d of standing (12.2 ± 0.1 h) on postprandial metabolism the following morning (30). Standing the previous day resulted in a lower fasting plasma triglyceride

concentration the next morning ($P = 0.02$). However, no difference between trials in incremental area under the curve (AUC) for PPTG was detected ($P > 0.05$). Furthermore, there were no differences in fat oxidation, plasma glucose concentration, or plasma insulin concentration (all $P > 0.05$). These data demonstrate that 12 h of standing compared with 14 h of sitting has only a small effect on the next day by lowering fasting plasma triglyceride concentration. For practical purposes, sitting and standing are both inactive, and subsequent fat metabolism is equally low. One nonsignificant but notable effect of standing was a 6% increase in metabolic rate.

How Many Steps Per Day Are Needed to Prevent Exercise Resistance?

Another study systematically reduced daily step number and identified the range of step counts that elicit exercise resistance (31). It thus determined how many steps per day are needed to maintain a healthy high rate of whole-body fat oxidation and a lowering of PPTG concentration. Simply put, we observed that ~8500 steps·d^{-1} was sufficient, whereas less than ~5000 steps·d^{-1} was not sufficient. Specifically, after 2 d of controlled activity, participants completed 2 d of low, limited, or normal steps (2675 ± 314, 4759 ± 276, and 8481 ± 581 steps·d^{-1}, respectively) (31) (Fig. 3). Participants then completed a 1-h bout of running on the evening of the second day, which served as the stimulus for evaluating exercise resistance. High-fat tolerance tests (*i.e.*, measure PPTG) were performed on the next morning, and postprandial responses were compared. After both low and limited, postprandial incremental AUC of plasma triglyceride was elevated 22%–23% compared with normal ($P < 0.05$). Whole-body fat oxidation was also significantly lower (16%–19%, $P < 0.05$, respectively) in low and limited compared with normal (Fig. 3). This indicates that exercise resistance occurs in individuals taking approximately 5000 or fewer steps per day, whereas 8500 steps·d^{-1} protects against exercise resistance in fat metabolism. Further studies are needed to compare step numbers between 5000 and 8500 steps·d^{-1}. Tudor-Locke and Bassett (32) estimated and proposed that less than 5000 steps·d^{-1} may be used as a "sedentary lifestyle index," which agrees remarkably well with our finding that exercise resistance occurs when taking less than ~5000 steps·d^{-1}.

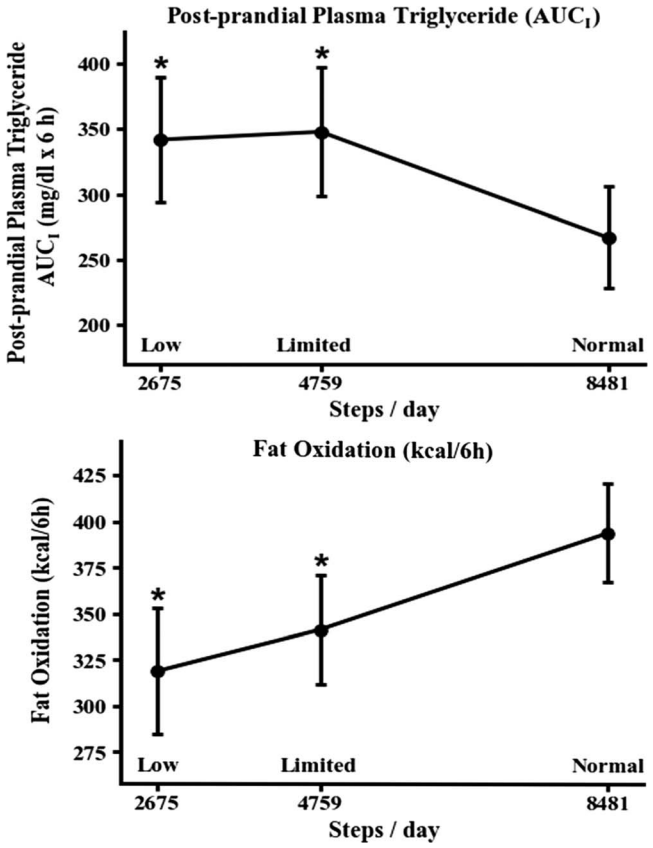

Figure 3. Relation between the level of physical activity in steps per day on the next day's fat metabolism measured during a 6-h postprandial measure of (A) postprandial plasma triglyceride concentration AUC incremental (AUC$_I$) and (B) fat oxidation over 6 h. The "normal" responses when having taken 8481 steps·d^{-1} the day before was a high rate of fat oxidation and a low level of plasma triglyceride concentration. On the contrary, when having taken either a low (2675 steps·d^{-1}) or limited (4,759 steps·d^{-1}), the PPTG was significantly elevated (top A) and fat oxidation significantly reduced (bottom B) compared with normal ($P < 0.05$) (31). *Low and limited are significantly different from normal ($P < 0.05$).

Interestingly, Lee *et al.* (33) found rates of mortality progressively declined with increasing daily steps until plateauing at approximately 7500 steps·d^{-1}. Recently, a similar pattern was reported by Saint-Maurice *et al.* (34), who observed a curvilinear relation with a mortality hazard ratio being twice as high in people taking 4000 steps·d^{-1} compared with those with 8000 steps·d^{-1}. These epidemiological studies agree well with our estimate that ~8500 steps·d^{-1} maintains healthy fat metabolism, yet ~5000 steps·d^{-1} is significantly lower. Contrary to our findings of no difference between low (*i.e.*, 2675) and limited (*i.e.*, 4759) in fat metabolism, Lee *et al.* (33) reported that groups taking 4363 steps·d^{-1} displayed reduced mortality compared with those taking 2718 steps·d^{-1}. It has been shown that reductions in daily step number for 1 wk have been associated with drastic increases in the AUC of plasma insulin during an oral glucose tolerance test, indicating development of insulin resistance (35). This supports the concept that the effects of inactivity are potent. As mentioned, inactivity can override even a strenuous 1-h bout of running and prevent it from improving fat metabolism the following morning.

Dynamic Nature of Fat Metabolism

It seems that fat metabolism is influenced more by the inhibitory effects of inactivity than by the stimulating effects derived from 1 h of moderate-intensity running. This is noteworthy because running for 1 h in the evening involves taking ~10,000 steps. However, as mentioned, it seems that those steps did not contribute to reversing exercise resistance, possibly because exercise resistance had already been established. In our model, exercise was performed in the evening of day 1 (Fig. 1), and when previously inactive, the 1-h run did not improve fat metabolism (Fig. 2B). Again, it seemed that exercise resistance had already set in after being inactive for approximately 24–48 h (Fig. 1). The only condition or exercise that seems to "break through" the exercise resistance of subjects taking only less than 4000 steps·d^{-1} was the interruption of prolonged sitting with hourly maximal "all-out" intensity cycling sprints of only 4-s duration (see below). In those cases, the brief hourly cycling sprints (5 × 4-s) were begun in the morning and continued until the evening (36). This suggests that the timing of exercise is important for offsetting exercise resistance and that the volume does not have to be large.

Can Interruption of Prolonged Sitting With 4-Second Cycling Sprints Prevent Exercise Resistance?

We next determined if the interruption of prolonged sitting (*i.e.*, 8 h of inactivity) with hourly maximal all-out intensity cycling sprints of only 4-s duration each (*i.e.*, 5 × 4-s sprints per hour × 8 h = 160 s·d^{-1} or 2.7 min·d^{-1} of "sprints") improve and normalize the PPTG response and fat oxidation (36). The 4-s sprints used an inertial load ergometer and were followed by 45 s of seated rest (36). People usually state that a major reason for not being physically active or exercising is lack of time (37). Therefore, a mode of exercise that is as brief as possible was investigated. Very brief exercise performed with maximal effort has the advantage of being capable of producing very-high power outputs (*i.e.*, 870 ± 139 W) and, thus, activation of a large number of motor units and muscle fibers. When sprints are performed maximally, both type I and type II muscle fibers are activated, and when the duration is very short (*i.e.*, 4 s), there is little fatigue (38). Thus, hourly 4-s sprints (5×) were performed. Again, the goal was not to perform a large volume of work but to repeatedly activate as many muscle fibers as possible during the 8-h period of prolonged sitting and determine if exercise resistance can be prevented. The next day's postprandial plasma triglyceride incremental AUC was reduced by 31% ($P < 0.01$) in the "sprint trial" compared with "sitting trial" for eight continuous hours (Fig. 4A). Furthermore, on the next day, the sprints had the effect of significantly ($P < 0.001$) increasing fat oxidation by an average of 43% ($P < 0.01$) over the duration of PPTG measurements (Fig. 4B). It was not possible to determine if the postprandial lowering of plasma triglyceride concentration was directly due to increased tissue uptake and oxidation of the ingested plasma triglycerides, but it seems plausible.

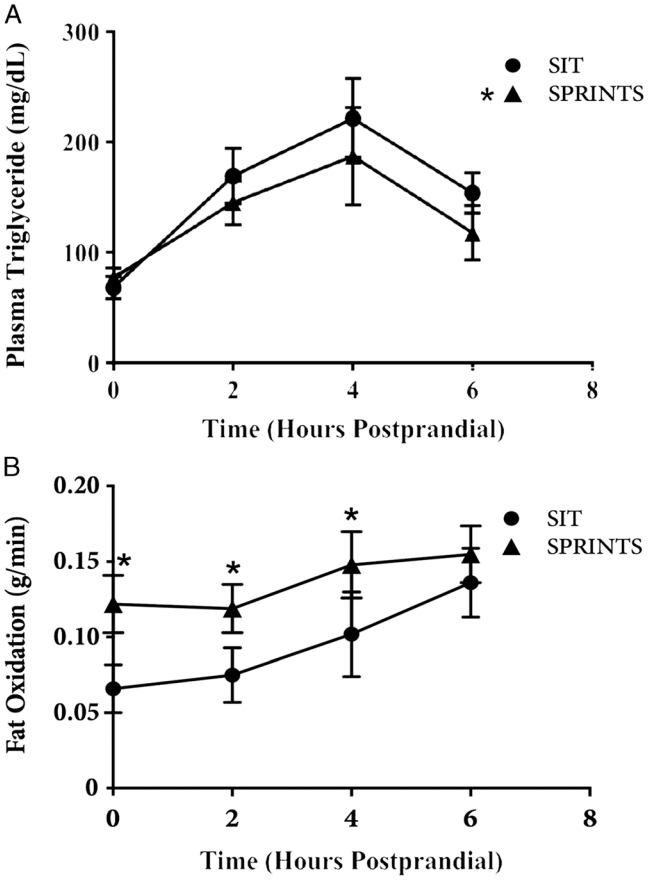

Figure 4. A. Plasma triglyceride concentration during the 6-h period after ingesting a high-fat meal the morning after subjects, on the previous day, either sat continuously for 8 h (SIT) or also sat for 8 h, but interrupted the sitting every hour with seated cycling SPRINTS of only 4-s duration performed five times with all-out effort. The SPRINT trial elicited a 31% reduction in the AUC of plasma triglycerides compared with SIT and a 43% elevation in fat oxidation (* $P < 0.01$). (Panel A reprinted from Wolfe AS, Burton HM, Vardarli E, Coyle EF. Hourly 4-s sprints prevent impairment of postprandial fat metabolism from inactivity. Med. Sci. Sports Exerc. 2020; 52(10):2262-2269. Copyright © 2020 American College of Sports Medicine. Used with permission). B. Corresponding levels of fat oxidation.

The mechanisms by which sprints caused a reduction in postprandial lipemia is not clear. Other studies that broke up prolonged sitting reported improved glucose and insulin metabolism during the time of increased activity (39), possibly because of the immediate effects of muscle contraction during the acute exercise. However, in our model, the improvement in postprandial lipemia is observed the following day at rest and during the resting PPTG measures (36). Metabolic effects that persist the day after the intervention, such as with fat metabolism, might be regulated in a more complex manner. The possible mechanism for an attenuation of postprandial lipemia is hypothesized to be related to mLPL increasing in the hours after exercise (17). Thus, it is feasible that the periodic interruption of sitting and a large amount of muscle fiber activation with sprints prevented exercise resistance and a decrease in mLPL activity during the 8-h period of sitting used by this investigation. It is noteworthy that this effect of sprints is achieved with only 20 s·h^{-1} (*i.e.*, 5 × 4-s sprints) of exercise, albeit at maximal power in 4-s bursts.

We have completed two training studies of 8-wk duration (3× per week) using repeated 4-s sprints (18–30×) while taking 15–45 s of recovery. This type of training elicits maximal power output that is four to six times above that needed to elicit $\dot{V}O_{2peak}$, and thus, both the anaerobic and aerobic systems are stressed (38). We have documented significant adaptations in young adults (40) and older adults (41) and found generally similar responses with increases in $\dot{V}O_{2peak}$, maximal power, and blood volume in young adults. It should be noted that high-intensity interval training is not inferior to moderate-intensity continuous training, and in some respects, it is superior and certainly more time efficient (42).

Does a Low Background of Physical Activity Attenuate Adaptations to Aerobic Training?

The studies presented above have found that exercise resistance acutely impairs fat metabolism, but the question remains as to whether it impairs other acute or chronic adaptations to exercise. We therefore determined if the level of background physical activity (steps per day) influences the short-term (five bouts of training over 9 d) whole-body adaptations to intense aerobic training while taking either ~4800 steps·d^{-1} (low steps (LS)) or ~16,000 steps·d^{-1} (high steps [HS]) (31,43) (Table 1). As expected, compared with the baseline measures, the HS group displayed a 31% and 27% reduction in plasma triglyceride excursion (AUC) during PPTG tests done after the first and last days of training ($P < 0.05$) (Table 1). Whole-body fat oxidation was also increased 24% and 19% compared with baseline in HS ($P < 0.05$) (Table 1). The benefits of training regarding fat metabolism seemed to be a "last bout effect" rather

TABLE 1. Percent changes from pretraining to posttraining as a result of short-term training in LS and HS groups (43).

	LS	HS
Variable	~4800 Steps·d^{-1}	~16,000 Steps·d^{-1}
Plasma triglyceride AUC; high fat tolerance test	−4.2% NS	−27%[a]
Resting fat oxidation	+6.0% NS	+19%[a]
Peak oxygen consumption	+7.2%[a]	+7.6%[a]
Responses during submaximal exercise at 79% $\dot{V}O_{2peak}$		
Heart rate	−2.7% NS	−6.6%[a]
Blood lactate concentration	0% NS	−11.8%[a]
Deoxy-hemoglobin	+4.7% NS	−7.4%[a]
Rating of perceived exertion	−7.6% ($P = 0.07$)	−12.2%[a]

[a] Significant improvement from pre- to posttraining ($P < 0.05$).

AUC, area under the curve; HS, high steps; LS, low steps; NS, nonsignificant.

than progressive improvement with subsequent bouts of training, as the responses after the last training bout were not better than after the first training bout. Furthermore, classic training adaptations were displayed by the HS group during submaximal and maximal exercise including significant decreases in submaximal heart rate, blood lactate levels, and muscle deoxygenated hemoglobin, as well as increased $\dot{V}O_{2peak}$ (*i.e.*, 7.6%) (Table 1).

Despite completing the same training program, the LS group did not show significant improvements in plasma triglyceride AUC during the PPTG tests or in fat oxidation. This agrees with findings that taking only ~4800 steps·d^{-1} elicits exercise resistance regarding fat metabolism (31) (Fig. 3B). What is particularly noteworthy is that LS did not display the classic training effects with no significant decreases during exercise at an absolute intensity in submaximal heart rate, blood lactate levels, and muscle deoxygenated hemoglobin. Yet, HS significantly improved all those measures. However, both LS and HS showed a 7%–8% increase in $\dot{V}O_{2peak}$. It seems that having a low level of background activity impairs some metabolic adaptations to short-term aerobic training in addition to the suppression of fat metabolism with nonsignificant changes in submaximal heart rate, blood lactate levels, and muscle deoxygenated hemoglobin. These adaptations are partly related to metabolic adaptations in muscle as is fat metabolism, raising the possibility that exercise resistance is largely a perturbation to muscle metabolism. The fact that LS and HS displayed similar significant increases in $\dot{V}O_{2peak}$ suggests that exercise resistance does not seem to influence cardiovascular factors such as stroke volume and a-vO_2 difference. The observations that a low background of activity (*i.e.*, LS) impairs or prevents improvement in submaximal heart rate, blood lactate levels, and muscle deoxygenated hemoglobin indicates that exercise resistance is a phenomenon that extends beyond impairing fat metabolism. However, it does not seem to blunt all training-induced adaptation because it did not attenuate the increase in $\dot{V}O_{2peak}$ with short-term training.

This implies that inactivity acutely impairs a number of bodily functions. It is interesting to note that people who are in the lowest levels of physical activity show precipitous increases in morbidity and mortality, yet the explanation for this is not clear. Certainly, the sickest people are the least able to be active. However, it is also likely that the least active people develop illnesses from phenomena not unlike that causing exercise resistance. Recent observations support the contention that additional metabolic factors can be influenced by reduced step number. Reduced myofibrillar protein synthesis can be seen in elderly and young healthy individuals in response to step reductions to ~1400 steps·d^{-1} over 2 wk or less (44). Taken together, it seems that reduced contractile activity for large periods of the day cause a condition in which current exercise or activity recommendations (1–3,5) may not be effective for deriving some protective health benefits of exercise such as improved fat oxidation and improved postprandial lipemia responses. Therefore, complete recommendations for physical activity also should consider the background levels of physical activity. Previous epidemiological studies suggest that remaining healthy may require ~7900 steps·d^{-1} (33), which is close to our estimate of at least 8500 steps·d^{-1} (31). However, we showed that if prolonged sitting throughout the day is interrupted hourly by 20 s of maximal cycling (5 × 4-s bouts), exercise resistance can be prevented at least in terms of fat metabolism (36). It thus seems that exercise resistance can be prevented not just by accumulating steps throughout the day but also by accumulating bouts of very short maximal-intensity exercise. This implies that accumulating at least 8500 steps·d^{-1} (31), although effective, is not the only method for preventing exercise resistance of fat metabolism. Walking or jogging for 8500 steps and approximately 6–7 km takes approximately 60 min. It seems that fat metabolism can remain high and exercise resistance can be prevented with only 2–3 min of exercise per day when performed all-out in 4-s bursts of cycling (36). It seems that the recommended methods for avoiding exercise resistance are varied.

Molecular Aspects

The molecular mechanisms by which inactivity decreases fat oxidation and elevates PPTG levels are not entirely clear. The amount of heparin releasable LPL and LPL's activity are decreased by up to 90% with inactivity, and this seems to be post-translational as mRNA is not reduced with inactivity (10,11). Studies with transcriptional inhibition indicate that the process of decreasing LPL during inactivity seem to be due to upregulation of a gene other than LPL that quickly turns off functional LPL activity found on the capillary endothelium (10,11). The effects of the transcriptional blockade were specific to the inactive group because there was no effect on LPL in standing/ambulatory rats (10,11). LPL was rapidly restored to normal within 4 h of intermittent standing and slow walking. It might be that LPL activity is downregulated by some metabolite (*e.g.*, GPIHBP1 protein endocytosis) induced during periods of prolonged inactivity (45). GPIHBP1 is the protein responsible for anchoring mLPL to the luminal surface of the capillary, and impairment of proper translocation could suppress mLPL activity without significant reductions in transcription (45).

Another metabolite to consider is thioredoxin-interacting protein (TXNIP). It was observed that 6 h of hindlimb immobilization in rats resulted in an increase in TXNIP protein expression and mRNA (46). Plasma triglyceride uptake by skeletal muscle is regulated by mLPL that is carried across endothelial cells. Whether the unhealthy elevation in PPTG with inactivity is related to an increase in TXNIP remains to be determined. However, another factor that makes the lowering of TXNIP an interesting candidate for the effectiveness of exercise and high

daily steps in preventing increases in PPTG is the observation that AICAR-induced AMPK activation prevents immobilization from increasing TXNIP (46). It is not known if AMPK activation from steps and sprints is sufficient to attenuate TXNIP and maintain a healthy level of fat metabolism. AMPK activation has been observed to induce LPL in skeletal muscle (47). Future studies using repeated maximal exercise are needed to test the hypothesis that AMPK activation prevents TXNIP elevation and allows a healthy increase in LPL activity to augment the uptake of plasma triglyceride into skeletal muscle and increase fat oxidation.

SUMMARY

Inactivity seems to be more than simply the lack of exercise, and through unknown mechanisms, it impairs fat metabolism from displaying its normally robust increase in fat oxidation and lowering of postprandial plasma TG the morning after exercise. This exercise resistance and blunting of fat oxidation may play a major role in the development of obesity. However, exercise resistance can be prevented by taking 8500 steps·d^{-1} or by interrupting 8 h of sitting with several hourly cycle sprints of only 4-s duration. A background of low daily steps during short-term aerobic training also significantly blunts some classic metabolic adaptations. This new perspective indicates an interplay between background physical activity (*e.g.*, steps or sprints) and exercise stimuli in regulating the acute and chronic metabolic adaptations to exercise. This also suggests that guidelines for recommending physical activity also should consider the background level of physical activity because it is possible for a person to meet the guidelines but still be exercise resistant if he or she is largely inactive most of the day.

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