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INVITED REVIEW

Changes in fat oxidation in response to various regimes of high intensity interval training (HIIT)

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Abstract Increased whole-body fat oxidation (FOx) has been consistently demonstrated in response to moderate intensity continuous exercise training. Completion of high intensity interval training (HIIT) and its more intense form, sprint interval training (SIT), has also been reported to increase FOx in different populations. An explanation for this increase in FOx is primarily peripheral adaptations via improvements in mitochondrial content and function. However, studies examining changes in FOx are less common in response to HIIT or SIT than those determining increases in maximal oxygen uptake which is concerning, considering that FOx has been identified as a predictor of weight gain and glycemic control. In this review, we explored physiological and methodological issues underpinning existing literature concerning changes in FOx in response to HIIT and SIT. Our results show that completion of interval training increases FOx in approximately 50% of studies, with the frequency of increased FOx higher in response to studies using HIIT compared to SIT. Significant increases in β-HAD, citrate synthase, fatty acid binding protein, or FAT/CD36 are likely responsible for the greater FOx seen in these studies. We encourage scientists to adopt strict methodological procedures to attenuate day-to-day variability in FOx, which is dramatic, and develop standardized procedures for assessing FOx, which may improve detection of changes in FOx in response to HIIT.

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Abbreviations

ATP	Adenosine triphosphate
β-HAD	β-Hydroxyacyl acyl-CoA dehydrogenase
CHOOx	Carbohydrate oxidation
CS	Citrate synthase
EPOC	Excess post-exercise oxygen consumption
FFA	Free fatty acid
FOx	Fat oxidation
HR_{max}	Maximal heart rate
HIIT	High intensity interval training
MFO	Maximal fat oxidation
MICT	Moderate intensity continuous training
RER	Respiratory exchange ratio
RQ	Respiratory quotient
SIT	Sprint interval training
VO_{2max}	Maximal oxygen uptake

Introduction

During exercise, carbohydrates (CHO) and lipids are the primary substrates oxidized in the mitochondria to support muscle contraction. It is apparent that during graded exercise, fat oxidation (FOx) increases from low intensities and typically peaks at a workload coincident with maximal fat oxidation (MFO), after which FOx declines and carbohydrate oxidation (CHOOx) becomes the primary source of ATP (Brooks and Mercier 1994). In 300 men and women completing progressive treadmill exercise, Venables et al. (2005) demonstrated that MFO occurs at a workload equal

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to 48% maximal oxygen uptake (VO_{2max}) and 61% maximal heart rate (HR_{max}).

A hallmark adaptation to long-term moderate intensity continuous training (MICT) is an increase in whole-body FOx and reduction in carbohydrate oxidation CHOOx. For example, Hurley et al. (1986) showed that 3 months of MICT led to substantial increases in whole-body FOx and a 41% reduction in muscle glycogen utilization during prolonged exercise. These improvements in FOx were attendant with increases in β-hydroxyacyl acyl-CoA dehydrogenase (β-HAD) activity (Hurley et al. 1986) and muscle oxidative capacity represented by greater mitochondrial mass and density (Holloszy and Coyle 1984). This greater reliance on FOx and resultant sparing of muscle glycogen is advantageous by improving tolerance to long-term exercise.

Fasting and exercise rates of substrate oxidation have also been implicated as measures of health and disease risk. Shook et al. (2015) reported that individuals with higher fasting respiratory quotient (RQ, a proxy of substrate oxidation at the cellular level), indicative of a greater portion of carbohydrates being oxidized, gained larger amounts of weight than individuals with lower RQ. This finding has been corroborated in 24-h metabolic chamber studies in which higher fed respiratory exchange ratio (RER) was positively associated with weight gain, 24 h fat oxidation was inversely associated with weight change (in men), and a higher 24 h RER was predictive of greater ad libitum food intake (Piaggi et al. 2013, 2015). In addition, FOx and the ability to switch between FOx and CHOOx (metabolic flexibility) have been implicated in development of type 2 diabetes (Kelley and Simoneau 1994) and metabolic syndrome (Storlien et al. 2004). Similarly, Robinson et al. (2015) demonstrated that the MFO is associated with insulin sensitivity in healthy men. In sum, these studies suggest that assessment of FOx may be useful as a clinical tool for risk assessment and stratification in various individuals.

Despite existing evidence showing that chronic MICT increases FOx as well as outcomes such as maximal oxygen uptake (VO_{2max}) (Duscha et al. 2005), insulin sensitivity (Houmard et al. 1993), and control of body weight (Donnelly et al. 2003) and blood pressure (Cornelissen et al. 2011), regular participation in MICT is quite low (CDC 2016). In the last 10 years, there has been increased attention towards the utility and efficacy of high intensity interval training (HIIT), brief (1–4 min) bouts of intermittent exercise at intensities ranging from 60 to 100 percent peak power output (PPO), on variables related to cardiometabolic health in various populations. In addition, the effects of low-volume sprint interval training (SIT) typically requiring ≤ 30 s "all-out" efforts at intensities greater than PPO have been examined (Gibala and McGee 2008). Data show that HIIT and SIT elicit similar and, in some cases, superior adaptations compared to MICT (Milanović et al. 2015).

Recently, numerous reviews have summarized VO_{2max} changes to HIIT or SIIT regimes in healthy adults (Bacon et al. 2013; Sloth et al. 2013; Weston et al. 2014a, b; Milanović et al. 2015) and clinical populations (Weston et al. 2014a, b). More recently, another review examined the role of number of SIT bouts on various health-related benefits (Vollaard et al. 2017). To our knowledge, no review has described changes in FOx in response to various HIIT regimes. Based on the link between FOx and metabolic health (Kelley and Simoneau 1994; Robinson et al. 2015) as well as a relative dearth of studies investigating changes in FOx in response to HIIT, a review documenting changes in FOx in response to HIIT, and highlighting physiological factors underpinning these adaptations is merited, with a goal to advance knowledge and present topics which remain to be addressed.

Change in fat oxidation in response to HIIT

Table 1 summarizes 27 studies in which changes in whole-body or resting FOx are reported in response to various HIIT regimes. Examination of these data shows that 62% (10/16) of studies employing HIIT and 37% (4/11) of studies employing SIT denote significant increases in FOx in response to training. However, only five studies included a control group, suggesting that the training-induced increases in FOx may not be clinically meaningful as they were not statistically compared to individuals who were not performing training. It seems that increased FOx occurs rapidly, as two studies report this adaptation after as little as six sessions of SIT (Astorino et al. 2011) and six (Talanian et al. 2010) or nine sessions of HIIT (Astorino et al. 2013). Increased exercise FOx occurs when the assessment includes a single low (Alkahtani et al. 2013) or moderate exercise intensity (Perry et al. 2008; Burgomaster et al. 2008; Talanian et al. 2007, 2010) as well as multiple submaximal intensities (Astorino et al. 2013; Lazzer et al. 2017), which suggests that this adaptation occurs across a wide range of work rates. In addition, gender may not influence the FOx response to training, as 75% of the studies showing significant changes included men and women, and Astorino et al. (2011) showed no difference in the FOx response to 2 weeks of SIT between men and women. In a recent study (Skelly et al. 2017), the acute signaling response (changes in genes associated with mitochondrial biogenesis) to SIT was mostly similar between men and women. Lastly, only four studies used treadmill walking or running, and their reported frequency of improvements in FOx (25%) is lower than that for studies requiring cycling.

The magnitude of change in whole-body FOx determined from RER seems to depend upon the specific HIIT protocol completed. Small but significant decreases in RER

Table 1 Summary of studies showing changes in fat oxidation in response to high intensity interval training

Study	Subjects	Protocol	Sessions	Intensity	Training time (min)	Control group	FOx measure	Finding
Alkahtani et al. (2013)	10 obese men	30–45 × 30 s bouts of HIIT	12	90% VO_{2max}	15–22.5	No	RER during 45 min of cycling at 45% VO_{2max}	↑ in MFO and FOx
Arad et al. (2015)	9 inactive obese women	4 × 30–60 s bouts of HIIT	42	75–90% HRR	2–4	Yes	RER during cycling at 40 W	ND in FOx
Aslankeser and Balci (2017)	8 women	2 bouts of SIT	10	Wingate test	1	Yes	RER during graded cycling	ND in MFO
Astorino et al. (2011)	20 active M and W	4–6 bouts of SIT	6	Wingate test	2–3	Yes	RER during 10 min of cycling at 50, 60, 70% PPO	↑ in FOx
Astorino et al. (2013)	20 inactive W	6–10 bouts of HIIT	36	60–90% PPO	6–10	Yes	RER during graded cycling	↑ in MFO and FOx
Astorino et al. (2017)	39 active M and W	Periodized HIIT or SIT	18	70–150% PPO	4–10	Yes	RER during graded cycling	No change in MFO but small ↑ in FOx
Bagley et al. (2016)	41 M and W	4 × 20 s bouts of SIT	36	175% VO_{2max}	1.3	No	RER during graded cycling	↑ in MFO
Burgomaster et al. (2006)	8 active M	4–7 bouts of SIT	6	Wingate test	2–3.5	Yes	RER during cycling at 60% VO_{2max}	ND in FOx
Burgomaster et al. (2008)	10 active M and W[a]	4–6 bouts of SIT	18	Wingate test	2–3	No	RER during 1 h cycling at 65% VO_{2max}	↑ in FOx
Cochran et al. (2014)	9 active M and W	1 4 min bout of HIIT	18	95% HR_{max}	4	No	RER during 1 h cycling at 65% VO_{2max}	ND in FOx
Gahreman et al. (2016)	12 overweight M[a]	60 × 8 s bouts of HIIT	36	85–90% HR_{max}	8	Yes	RER during graded cycling	↑ in FOx
Gorostiaga et al. (1991)	6 inactive M and W[a]	20 × 30 s bouts of HIIT	24	100% PPO	10	No	RER during 20 min at 50% VO_{2max}	↑ in FOx
Guadalupe-Grau et al. (2017)	11 M and W with metabolic syndrome	4 × 4 min bouts of HIIT	72	90% HR_{max}	16	No	RER during graded cycling	↑ in MFO
Kohn et al. (2011)	18 endurance trained M	5 × 2.7 min bouts of HIIT	12	94% peak run speed	13	No	RER during graded running	ND in RER
Lanzi et al. (2015)	9 obese men[a]	10 × 60 s of HIIT	8	90% HR_{max}	10	No	RER during graded cycling	↑ in MFO and FOx
Larsen et al. (2015)	10 inactive M and W	5 × 60 s bouts of SIT	18	128% PPO	5	No	FOx in mitochondria	ND in FOx
Lazzer et al. (2017)	10 obese boys[a]	6 × 40 s bouts of HIIT	15	100% VO_{2max}	4	No	RER during treadmill walking	↑ in FOx
Martins et al. (2016)	32 inactive M and W[a]	30–60 × 8 s bouts of HIIT	36	85–90% HR_{max}	10–20	No	Resting RER	ND in resting FOx

Table 1 (continued)

Study	Subjects	Protocol	Sessions	Intensity	Training time (min)	Control group	FOx measure	Finding
Nybo et al. (2010)	8 inactive M[a]	5 × 2 min bouts of HIIT	24	95% HR_{max}	10	Yes	RER during walking and running	ND in FOx
Perry et al. (2008)	8 active M and W	10 × 4 min bouts of HIIT	18	90% VO_{2max}	40	No	RER during 60 min at 60% VO_{2max}	↑ in FOx
Schubert et al. (2017)	24 active M and W	6–8 × 1 min bouts of HIIT or 3–5 × 20 s bouts of SIT	12	HIIT = 90% PPO SIT = 5% BW (~ 250% PPO)	6–8 (HIIT); 1–1.67 (SIT)	Yes	RER during graded cycling	ND in MFO or FOx
Shepherd et al. (2013)	8 young inactive M[a]	4–6 bouts 30 s bouts of SIT	18	Wingate test	2–3	No	RER during 60 min of cycling at 65% VO_{2max}	ND in FOx;↑ in net IMTG breakdown
Støa et al. (2017)	19 M and W with diabetes	4 × 4 min bouts of HIIT	36	85–95% HR_{max}	16	No	RER during 10 min of walking at 60% VO_{2max}	ND in FOx
Talanian et al. (2007)	8 active W	10 × 4 min bouts of HIIT	7	90% VO_{2max}	40	No	RER during 60 min of cycling at 65% VO_{2max}	↑ in FOx
Talanian et al. (2010)	10 inactive W	10 × 4 min bouts of HIIT	18	90% VO_{2max}	40	No	RER during 60 min of cycling at 65% VO_{2max}	↑ in FOx
Whyte et al. (2010)	10 obese M	4–6 bouts of SIT	6	Wingate test	2–3 min	No	Resting RER	ND in resting FOx
Zinner et al. (2016)	16 active M	4–6 bouts of SIT	6	Wingate test	2–3 min	No	RER during cycling at 80 W	ND in FOx

M men, *W* women, *HIIT* high intensity interval training, *HRR* heart rate reserve, *SIT* sprint interval training, *PPO* peak power output, *RER* respiratory exchange ratio, *MFO* maximal fat oxidation, *FOx* fat oxidation, *HR* heart rate, *IMTG* intramuscular triglyceride

[a]The sample size reported here denotes the number of subjects who completed HIIT/SIT within a study in which other modes including MICT or resistance training were performed

(0.01–0.03 units reflecting 3–10% increases in FOx) were shown in response to six (Astorino et al. 2011) and 18 sessions of Wingate-based SIT (Burgomaster et al. 2008). However, in another study (Burgomaster et al. 2006) using the identical six session Wingate regime, no change in exercise RER was shown. A discrepancy in FOx responses between studies could be due to different exercise duration and intensity characteristic of the assessment used to determine RER. For example, in two studies (Burgomaster et al. 2006, 2008), moderate cycling elicited RER values ~ 0.96, at which determinations of fat and CHO oxidation are likely affected by production of non-metabolic CO_2 via bicarbonate buffering. Larger increases in FOx were shown with greater duration or volume of HIIT. For example, 16–26% increases in exercise FOx accompanied by a 20% increase in MFO were demonstrated in inactive young women undergoing 12 weeks of HIIT (Astorino et al. 2013). A similar magnitude of change in whole-body fat oxidation equal to 10–20% (in the form of a 0.03–0.05 reduction in RER) was shown in active women undergoing seven sessions of high-volume HIIT (Talanian et al. 2007), active (Perry et al. 2008) and inactive women performing 6 weeks of high volume HIIT (Talanian et al. 2010), and men and women undergoing 12 weeks of low-volume SIT (Bagley et al. 2016). In the Talanian et al. (2010) and Astorino et al. (2013) studies, FOx did not increase after the early phase of HIIT, suggesting that in inactive and active women, a greater amount of training may not elicit additional increases in FOx.

A relatively unexplored area is whether individual non-response to HIIT may occur, in that some participants may be classified as "responders" as well as "non-responders" to training. Results from the HERITAGE study (e.g. Bouchard et al. 1999) showed individual responses to 20 weeks of MICT for outcomes including VO_{2max}, heart rate, and blood pressure. Similarly, recent studies document individual responses to HIIT and SIT (Astorino and Schubert 2014; Gurd et al. 2016). For example, in response to 2 weeks of SIT or 12 weeks of HIIT, Astorino and Schubert (2014) reported that only 65% of participants exhibit increases in whole-body FOx represented by changes greater than the day-to-day variability in the measure. In both studies, changes in FOx were significantly and inversely correlated with baseline VO_{2max}. In 189 adults with enhanced risk of type II diabetes, Phillips et al. (2017) reported widely variable changes in VO_{2max} (− 79 to + 587 mL/min) and mean arterial pressure (− 9.0 to + 4.0 mm Hg) in response to 6 weeks of HIIT. This is an important topic to investigate, considering the desire to personalize exercise programs to optimize health and fitness-related adaptations.

A description of changes in FOx in response to HIIT would not be complete without a brief description of post-exercise increases in FOx in response to a single bout of HIIT or SIT. It is apparent that oxygen uptake is elevated after intense exercise for 1 (Tucker et al. 2016) or more hours (Greer et al. 2015) and, in some cases, up to a few days (Schuenke et al. 2002), and that intense exercise (Gore and Withers 1990) tends to elevate this excess post-exercise oxygen consumption (EPOC) more than MICT. During recovery from moderate to intense exercise, RER is typically depressed due to glycogen depletion as well as a restoration of the bicarbonate pool (Laforgia et al. 1997). McGarvey et al. (2005) showed a lower post-exercise RER in response to HIIT (repeated 3 min bouts at 90% VO_{2max}) versus MICT (65% VO_{2max}), which would suggest enhanced FOx. Chan and Burns (2013) showed a 75% increase in FOx after a single session of Wingate-based SIT, but this was compared to a non-exercise control condition rather than another exercise mode such as MICT. In contrast, results from another study in 18 men (Williams et al. 2013) showed no difference in post-exercise FOx or EPOC between 60 min of MICT at 65% VO_{2max} and SIT (4 Wingate tests). This would suggest that SIT is not superior to MICT for enhancing FOx up to 3 h post-exercise. Skelly et al. (2014) showed elevated VO_2 for up to 24 h after completion of HIIT (10 60 s bouts at 90% HR_{max}) and MICT (50 min at 70% VO_{2max}), yet there was no difference in RER. When 9 men completed a control condition and three SIT sessions of matched exercise volume and recovery but differing in bout duration (5, 15, and 30 s bouts) (Islam et al. 2017), data showed that post-exercise FOx was highest in response to the 15 and 30 s versus the 5 s bout and control session. Overall, data show that HIIT or SIT increases FOx post-exercise compared to resting, and longer bouts may be preferable to enhance FOx versus shorter bouts.

Finally, there is the possibility that HIIT or SIT may influence resting FOx. However, this has not been thoroughly investigated. For example, Martins et al. (2016) reported that 12 weeks of HIIT, MICT, or reduced volume HIIT did not significantly affect FOx in sedentary and obese individuals. When Schubert et al. (2017) compared 4 weeks of HIIT and SIT in active men and women, they also observed no significant changes in resting FOx, although resting metabolic rate was increased. In contrast, in response to 2 weeks of Wingate-based SIT, Whyte et al. (2010) reported increases in FOx ~ 24 h post-exercise, but not 72 h post-intervention. Minimal changes in resting FOx may not be widespread in response to training due to heavy reliance on fat metabolism at rest (Saris and Schrauwen 2004). Further research should explore this line of inquiry, as resting FOx is related to propensity for weight gain (Shook et al. 2015), but care must be taken to avoid the transient effects of HIIT and SIT.

Physiological factors mediating changes in fat oxidation in response to HIIT

Recently, MacInnis and Gibala (2017) described that mitochondrial content is enhanced after only 6–7 sessions of HIIT, which is related to greater capacity for FOx with HIIT or SIT. At least three mechanistic reviews concerning regulation of FOx (Spriet 2002; Bonen et al. 2002; van Hall 2015) have been previously published, so we will not present extensive content in this review concerning the physiological factors determining FOx. Nevertheless, it is necessary to denote that regulation of FOx includes (1) adipose tissue lipolysis and FFA transport to muscle, (2) FFA movement across the muscle membrane via fatty acid binding protein ($FABP_{pm}$) and FAT/CD36, (3) regulation of activity of muscle triglyceride (TG) lipase or hormone sensitive lipase (HSL), and (4) regulation of FFA movement across the mitochondrial membranes via carnitine palmitoyl transferase I (CPT-I) (Spriet 2002). In addition, as FFA are ultimately burned in the mitochondria through beta-oxidation and subsequently the Kreb's cycle and electron transport chain, alterations in enzymes including β-HAD, citrate synthase (CS), and cytochrome c oxidase (COX) as well as protein expression such as peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) may enable the increased FOx seen with HIIT.

Increased mitochondrial content is commonly reported in response to HIIT. Tremblay et al. (1994) demonstrated that 15 weeks of HIIT led to significant increases in β-HAD, malate dehydrogenase, and CS as well as hexokinase and phosphofructokinase, reflecting enhanced glycolytic activity. In active women, increases in β-HAD (32%), total muscle $FABP_{pm}$ (25%), and CS (20%) were also shown in response to seven sessions of HIIT (Talanian et al. 2007). When the duration of this identical high-volume HIIT regime was extended to 6 weeks, significant increases in FAT/CD36 protein content were shown as well as increases in $FABP_{pm}$, CS, COX, and β-HAD (Perry et al. 2008). However, there was no change in HSL content in either study, which suggests that this adaptation may not be necessary to enhance FOx unlike increases in β-HAD and $FABP_{pm}$, which were shown in both studies. Interestingly, Talanian et al. (2010) showed that 6 weeks of high volume HIIT increased muscle HSL content, which was accompanied by increases in β-HAD, whole muscle and sarcolemmal $FABP_{pm}$, and whole muscle and mitochondrial FAT/CD 36 content. Data from these studies also suggest that a greater training volume may be needed to enhance FAT/CD36 content, as it was only increased in response to 18 and not 7 sessions of HIIT. Unfortunately, to our knowledge, no study has investigated changes in these proteins in response to longer-term HIIT or clarified their decay in response to de-training.

Fat oxidation is partially regulated by release of norepinephrine and epinephrine (Spriet 2002), yet only a few studies have determined alterations in these hormones with HIIT. In runners, Billat et al. (1999) showed no change in norepinephrine levels in response to interval training at VO_{2max}. Nevertheless, lower epinephrine levels were reported in active women who completed short-term HIIT (Talanian et al. 2007), which would be expected to reduce glycogen utilization and potentially augment FOx. In fact, significantly higher whole-body FOx was reported by these authors (Table 1), which suggests a potential role of a blunted epinephrine response to enhance FOx after HIIT.

Many studies have also examined changes in regulators of FOx in response to various regimes of SIT. Parra et al. (2000) showed that 14 sessions of SIT led to significant increases in CS and β-HAD activity whether training was performed consecutively or with regular rest. Two weeks of Wingate-based SIT (Burgomaster et al. 2006) led to a significant increase in CS, yet no change in β-HAD or whole-body FOx. Six weeks of SIT led to early (1 week) and sustained increases in COX, yet no change was shown in FAT/CD36 or $FABP_{pm}$ (Burgomaster et al. 2007). Since FOx seems to be primarily limited by CPT-1 activity (McGarry and Brown 1997), it may not be essential for increases in fatty acid transport to occur in response to training. A follow-up study (Burgomaster et al. 2008) showed significant increases in CS, β-HAD, and PGC-1α in response to 6 weeks of SIT which were accompanied by a small but significant increase in whole-body FOx. Lastly, results from Allemeier et al. (1994) showed that 6 weeks of SIT consisting of three Wingate tests separated by 20 min rest per session led to significant increases in myosin heavy chain type IIa content and decreases in myosin heavy chain IIb content. This specific adaptation would potentially enhance reliance on aerobic metabolism and in turn, enable a greater contribution of FOx.

Nevertheless, a few studies report no changes in FOx after SIT. Schubert et al. (2017) reported no change in resting and exercise FOx or MFO in active men and women completing 12 sessions of SIT (repeated sprints at 5% BW), which supports other data (Zinner et al. 2016). Vincent et al. (2015) reported no change in PGC-1α in response to eight sessions of single-leg SIT at 120% PPO. However, increased CS activity as well as oxidative phosphorylation capacities were shown. These data suggest that mitochondrial content but not always protein expression is enhanced with SIT. Previous SIT studies included male and female participants (Burgomaster et al. 2008; Astorino et al. 2011), which suggests that gender does not seem to influence mitochondrial responses to HIIT/SIT. Although, Scalzo et al. (2014) demonstrated greater mitochondrial protein synthesis in men versus women in response to 9 days of SIT despite similar increases in CS and PGC-1α between genders. Similarly,

Gillen et al. (2014) showed that men and not women experienced significant increases in β-HAD in response to extremely low-volume SIT, although increases in CS and COXIV protein content were similar between genders. Overall, strict consideration of factors including menstrual cycle, body composition, and relative fitness level is needed to better understand potential gender differences in the FOx response to interval training.

In young inactive men, Shepherd et al. (2013) examined changes in RER, intramuscular triglyceride (IMTG) oxidation, and insulin sensitivity in response to 6 weeks of Wingate-based SIT or MICT. Their data showed that MICT but not SIT led to a reduced RER during prolonged cycling, suggesting increases in whole-body FOx only in response in high-volume endurance training. Yet, both regimes enhanced insulin sensitivity as well as upregulated expression of perilipin 2 and 5 (PLIN 2 and PLIN5), which have been shown to be related to IMTG derived lipolysis (Bell et al. 2008). When obese men completed 4 weeks of SIT or MICT (Shepherd et al. 2017), insulin sensitivity and expression of PLIN2 and PLIN5 were enhanced with both regimes and there was a reduction in ceramide levels, which have been shown to be inversely related to insulin sensitivity (Straczkowski et al. 2007). As insulin sensitivity is positively related to exercise FOx (Robinson et al. 2015), this has a potential impact on improving FOx although further study is needed to verify this result.

Variability in fat oxidation measures

One challenge in detecting training-derived changes in FOx in response to an intervention such as HIIT is the potential variability in the measure. In male and female cyclists (VO_{2max} = 55.9 mL/kg/min, range = 42.0–70.0 mL/kg/min), RER at rest and during steady-state exercise showed marked variability (Goedecke et al. 2000). For example, at a workload equal to 50% PPO, RER ranged from 0.82 to 0.98 across subjects. In 305 healthy adults withVO_{2max} equal to 49.9 mL/kg/min who completed progressive treadmill exercise, mean MFO was equal to 0.55 g/min, yet ranged from 0.19 to 1.13 g/min across participants (Fletcher et al. 2017). These studies document the heterogeneous nature of exercise-derived measures of FOx and MFO in relatively homogeneous populations. When progressive cycling was performed twice by 15 healthy men with VO_{2max} equal to 52 mL/kg/min, marked variability in FOx and MFO was shown across days (Croci et al. 2014). The coefficient of variation for exercise FOx ranged from 24 to 49%; similarly, a high CV for MFO was evident (23–26%) despite this value differing by no more than 0.01 g/min between tests. Remarkably, these findings occurred despite low variability (< 5%) in exercise RER. When 16 active men and women completed two bouts of graded treadmill exercise (DeSouza Silveira et al. 2016), results demonstrated similar MFO between tests equal to 0.58 and 0.60 g/min which occurred at HR equal to 143 and 140 b/min. They reported an ICC for MFO across days equal to 0.90 and coefficient of variation equal to 7%, which is similar to values reported in other investigations (Perez-Martin et al. 2001 equal to 11%; Michallet et al. 2008, up to 12%). Nevertheless, in each study, dietary patterns and physical activity were only monitored for 1 day before graded exercise, which may be inadequate to standardize basal levels of muscle glycogen, plasma FFA, and blood lactate concentration. In addition, a limitation of these studies to identify and elucidate the noise or potential error in determinations of FOx is that these tests were completed 2–3 days (DeSouza Silveira et al. 2016) and 3–7 days (Croci et al. 2014) apart, rather than several weeks apart as would be followed in a training study. Whether similar variability in FOx exists when tests are repeated over a longer time span is unknown. In the case of the DeSouza Silveira et al. (2016) study, it is possible that the energy expenditure and glycogen degradation characteristic of the first exercise protocol could alter substrate metabolism in the second bout conducted as soon as 47 h after the initial session. This is supported by studies showing prolonged elevations in VO_2 after intense exercise such as HIIT (Laforgia et al. 1997) or strength training (Schuenke et al. 2002).

The considerable variability in FOx previously-reported (Croci et al. 2014) raises the question as to what a meaningful change in FOx would represent. The lack of an established value for this parameter opposes minimum improvements in VO_{2max} (1 MET), blood pressure (− 5 mmHg), blood glucose (− 1 mM), and waist circumference (− 7 cm) which have been shown to be predictive of improved health status (National Cholesterol Education Program 2002). In a recent study from our lab (Astorino et al. 2017), 39 men and women completed 6 weeks of periodized HIIT and another 32 men and women matched for physical activity and VO_{2max} served as non-exercising controls. Data from the controls who completed two bouts of progressive cycling 6 weeks apart showed no difference in MFO between pre- and post-testing (0.32 ± 0.08 g/min versus 0.31 ± 0.08 g/min) and ICC = 0.82. Standard error of the measurement and minimum difference for MFO were equal to 0.03 and 0.09 g/min, respectively. Since our mean pre-training MFO value was equal to 0.30 g/min, a meaningful change in MFO with HIIT may be as high as 30%. However, these values are likely only applicable to the specific participants tested and methodological procedures utilized in our laboratory, so we encourage other scientists to devise their own criteria to better portray if observed changes in FOx are clinically meaningful.

Methodological factors affecting changes in fat oxidation in response to HIIT

Table 1 shows that FOx is typically measured during prolonged exercise at a single submaximal intensity equal to 60–65% VO_{2max} (Burgomaster et al. 2006; Perry et al. 2008) or during multiple submaximal stages below, including, and above the MFO (Astorino et al. 2013, 2017; Lanzi et al. 2015; Lazzer et al. 2017). Although a standard stage duration has yet to be identified, Achten et al. (2002) showed that 3 min stages yielded similar estimates of FOx in cyclists compared to 5 min stages. In sedentary middle aged adults, Bordenave et al. (2007) reported that 3 min stages overestimated FOx, and that longer 6 min stages are preferable to accurately determine substrate oxidation during graded exercise. Another consideration is the exact approach used to identify MFO.

The proper determination of FOx rates and identification of MFO are crucial to enable accurate interpretation of data. Similar to use of various protocols for assessing FOx, there is no consensus for determining rates of FOx and MFO. One approach is to calculate rates of FOx via stoichiometric equations (Frayn 1983; Jeukendrup and Wallis 2005) using VO_2 and VCO_2 data and plot these values against exercise intensity. Analytical techniques include the fitting of a third polynomial function (P3) (De Souza Silveira et al. 2016; Croci et al. 2014), a sine-wave model (SINE) (Chenevière et al. 2009; Croci et al. 2014), and measured values (Croci et al. 2014). It seems that P3 and SINE appear to be the most accurate and sensitive methods, as they utilize forecasting and curve-fitting for FOx values and are preferred to estimating FOx simply from RER. The sampling frequency (breath-by breath, 10, 15, or 30 s averaging) also varies between studies, and in turn, this would influence the values of VO_2 and VCO_2 and in turn FOx and MFO, with shorter durations likely providing higher values (Midgley et al. 2007). Lastly, there is no consensus as to the amount of data analyzed from each exercise stage, as this duration ranges from 1 (Astorino et al. 2017), 2 (Venables et al. 2005; Astorino et al. 2013; Croci et al. 2014), and 3 min (Achten et al. 2002) to as long as 5 min (Goedecke et al. 2000; Talanian et al. 2010). Nevertheless, this duration should not alter the accuracy of estimates of fuel use as long as a steady-state is attained during each exercise stage.

Previous studies have highlighted various factors altering exercise FOx which must be recognized and carefully considered by scientists if training-induced changes in this outcome are properly assessed. Goedecke et al. (2000) examined determinants of resting and exercise RER in trained cyclists who completed prolonged exercise at 25, 50, and 70% PPO. Data showed that plasma concentrations of FFA, muscle glycogen content, blood lactate concentration, and fiber type predicted fat and CHO oxidation at rest and at each intensity. There was also wide variability in resting RER (0.72–0.93) which led to considerable variability in exercise RER, so the authors commented that resting RER could predict the pattern or magnitude of change in RER during exercise.

Exercise mode is another factor which may alter FOx responses to HIIT or SIT. It is apparent that treadmill exercise results in higher FOx versus cycling in trained (Achten et al. 2003) as well as relatively untrained individuals (King et al. 2016), which is explained by the higher force needed in cycling relative to running. Examination of Table 1 shows that only four studies have reported changes in FOx during treadmill exercise. Overall, it would be interesting to know if HIIT-mediated increases in FOx induced from one mode of exercise, such as cycling, can transfer over to treadmill walking or running. This line of inquiry is compelling since the physical activity patterns of most individuals are likely not relegated to a single exercise mode as typically used in laboratory studies (Fig. 1).

Standardization of dietary patterns and physical activity of study participants

It is apparent that alterations in dietary intake and physical activity modify concentrations of glycogen and FFA (Goedecke et al. 2000) and resultant substrate oxidation (Patterson and Potteiger 2011), so scientists need to closely monitor these behaviors to ensure stable substrate concentrations before assessment of FOx. Results from a recent study showed that, though small (~ 3%), prior CHO and fat intake over the 4 days before testing influenced the variability of MFO (Fletcher et al. 2017). Additional lack of dietary control may have also contributed to the considerable variability in FOx and MFO previously reported by Croci et al. (2014) and De Souza Silveira et al. (2016). Both studies utilized self-reported food logs which are prone to under-reporting (Archer et al. 2013) leading to altered substrate concentrations. Ideally, the research team would provide the participants with an evening meal that mimics habitual diet, but as Jeacocke and Burke (2010) recommend in their comprehensive review, the researchers should perform a cost-benefit analysis to determine the method best suited for them and within their resources, and also be prepared to thoroughly justify their choices. From a pragmatic standpoint, investigators can use the Institute of Medicine's Estimated Energy Requirement (EER) calculator to establish an estimated caloric intake for a participant's mass, height, age, sex, and activity level. This value could then be divided by 30% to yield an estimated number of calories for an evening meal. Macronutrient intake should mirror the habitual diet. For example, if the participant's EER is 3000 kcal/day, and their habitual diet is approximately 55/30/15% CHO, FAT,

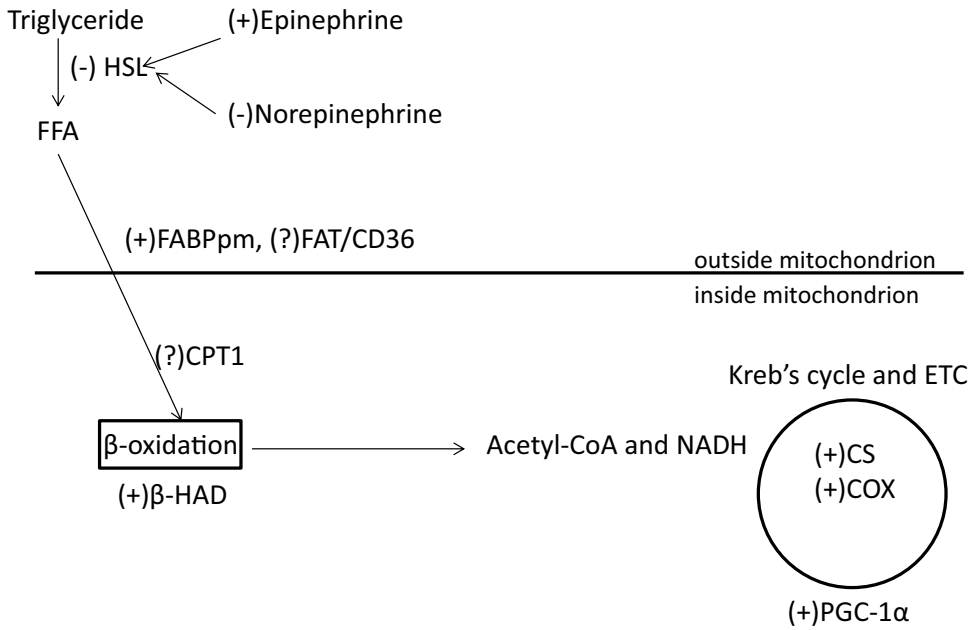

Fig. 1 Schematic representing mechanisms by which HIIT and SIT seem to enhance exercise FOx; symbol (plus) indicates that HIIT upregulates this step regulating fat oxidation; symbol (minus) indicates that HIIT does not affect this step regulating fat oxidation; symbol (question mark) indicates that HIIT may or may not affect this step regulating fat oxidation. *HSL* hormone sensitive lipase, *FFA* free fatty acid, *CPT1* carnitine palmitoyl transferase 1, *β-HAD* beta hydroxyl acyl CoA dehydrogenase, *CS* citrate synthase, *COX* cytochrome c oxidase, *PGC-1α* peroxisome proliferator-activated receptor gamma coactivator 1-alpha 1

and protein, then their evening meal should be ~ 1000 kcal (138 g CHO, 33 g FAT, 38 g PRO).

In addition, participants are frequently asked to abstain from physical activity for 24 h before testing which is confirmed through a written document or verbal affirmation, but again, this is not as exact or precise as an approach including accelerometry. Fletcher et al. (2017) reported that the primary determinants of MFO in healthy adults were VO_{2max}, sex, and physical activity (PA); however, these authors used self-reported PA rather than accelerometry and did not examine PA based on time spent in light, moderate, or vigorous exercise. Thus, one can only speculate about the appropriate guidelines for participants regarding pre-testing physical activity, but following recommendations similar to those established for assessment of resting metabolic rate (Compher et al. 2006; Fullmer et al. 2015) would be prudent.

This review raises many areas that require additional investigation. First, if investigators are going to determine changes in FOx in response to HIIT, standardized methods regarding the characteristics of the exercise test, data analytic procedures, and participant status need to be developed. In addition, although increases in FOx have been shown in response to both HIIT and SIT, additional study is merited to examine if they elicit similar improvements in FOx, which applies to patient populations desiring to augment their ability to oxidize fat. In addition, the optimal duration, intensity, and/or frequency of HIIT or SIT leading to increases in FOx is unknown, and although many mechanisms have been identified, additional inquiry is needed especially in clinical populations. Lastly, as day-to-day variability in FOx is so dramatic, work is needed to identify the source(s) of this variability and develop proper methods to ensure that changes in FOx seen after training are truly a response to exercise and not masked by biological error.

Conclusions

Overall, existing results suggest that HIIT and SIT increase whole-body FOx similar in magnitude to that previously reported in response to high-volume MICT (Holloszy and Coyle 1984; Hurley et al. 1986). Nevertheless, an increase in FOx is not as frequently-reported as improvements in VO_{2max} which are almost universally documented in response to HIIT and SIT (Bacon et al. 2013; Sloth et al. 2013). One weakness of the existing literature is that only a few studies have employed a non-exercising control group, and due to the dramatic day-to-day variability in FOx previously documented, it seems premature to state with certainty that HIIT consistently and meaningfully improves FOx. Adaptations responsible for any potential increases in FOx include enhanced oxidative capacity represented by activities of mitochondrial enzymes involved in the oxidation and transport of lipids as well as enhanced protein content of PGC-1α as well as PLIN2/PLIN5. Future research should focus on standardizing the exercise protocol used for assessing FOx and MFO as well as controlling participants' physical activity and dietary intake completed prior to FOx assessment. Data from these experiments would hopefully reduce the within-subject variability of FOx and MFO, and allow researchers to determine the minimal clinically important difference (MCID). Once the MCID has been identified, more research into individual responses could be

conducted, permitting researchers to determine the patterns of individual FOx and MFO response/non-response to HIIT and SIT.

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