Review

Impact of high-intensity interval training and sprint interval training on peripheral markers of glycemic control in metabolic syndrome and type 2 diabetes

Alberto Jiménez-Maldonado⁎, Patricia C. García-Suárez, Iván Rentería, José Moncada-Jiménez, Eric P. Plaisance

a Facultad de Deportes Campus Ensenada, Universidad Autónoma de Baja California, Mexico
b Human Movement Sciences Research Center, University of Costa Rica, San José, Costa Rica
c Department of Human Studies, University of Alabama at Birmingham, Birmingham, AL, United States of America

ARTICLE INFO

Keywords:
Glycemic control
Metabolic syndrome
Type 2 diabetes
Interval exercise training

ABSTRACT

Glycemic control is essential to reduce the risk of complications associated with metabolic syndrome (MetS) and type 2 diabetes (T2D). Aerobic and resistance exercise performed alone or in combination improve glycemic control in both conditions. However, perceived lack of time and commitment are considered principal barriers to performing exercise regularly. High intensity interval training (HIIT) and sprint interval training (SIT) can be performed in a fraction of the time required for continuous aerobic exercise. A substantial scientific evidence indicates that HIIT/SIT improve glycemic control to a similar or greater extent than aerobic exercise in populations without MetS or T2D. Likewise, growing evidence suggest that HIIT/SIT improve the glycemic control during MetS and T2D. The aim of this review is to discuss the effects of interval training protocols on peripheral markers of glucose metabolism in patients with MetS and T2D.

1. Introduction

Incidence of metabolic syndrome (MetS) and type 2 diabetes (T2D) in adults over age 18 continues to rise in developed and under-developed countries around the world [1,2]. The economic burden of diabetes and diabetes-related healthcare has been estimated at approximately $327 billion dollars annually in the United States [3]. Barceló et al. reported per capita diabetes-related loss of productivity due to mortality at approximately $593 and morbidity at $186 dollars annually in Latin American and Caribbean countries [4]. Furthermore, the combined expenditures for Latin American and Caribbean countries exceeds $10 billion dollars per year for treatment of T2D [4], a level of economic burden that is unsustainable. In fact, the International Diabetes Federation indicates that health-related expenditures for T2D range from 5 to 20% of total healthcare expenditures [5]. In just over 10 years, from 2009 to 2020, annual healthcare expenditures for patients with MetS rose by 59% in Germany [6], shedding further light on the economic challenges that lie ahead. Others report that in the United States the average annual cost of treating patients with MetS is over 1.6 times greater in patients with MetS compared to those without MetS [7,8].

MetS and T2D are often characterized by insulin resistance with resulting hyperglycemia [9] (Fig. 1). Chronic hyperglycemia leads to severe inflammatory, metabolic, and cardiovascular responses that increase risk of morbidity and mortality [10-18]. Therefore, glycemic control is one of the cornerstones for treatment in these populations [19,20]. In response, traditional and emerging pharmacological and lifestyle strategies such as physical activity and diet continue to be investigated to attenuate the burden of these metabolic disease conditions [9,21,22].

The American Diabetes Association (ADA) recommends at least 150 min/week of moderate-intensity continuous physical activity or 75 min/week of vigorous-intensity physical activity for all individuals [9,21]. However, sedentary behavior and perceived lack of time are the primary reasons reported for not exercising regularly [23,24]. Innovative exercise regimens such as high-intensity interval training (HIIT) and sprint interval training (SIT) use short-term (30s-4min) near-maximal to maximal exercise intensity with moderate-intensity or passive rest intervals. HIIT and SIT have become increasingly popular and the vast majority of scientific evidence indicates that either form of...
Interval training produces similar or even superior metabolic and physiological adaptations compared with moderate intensity continuous training (MICT) [25–28]. These findings are important since HIIT and SIT require 60–90% less time than MICT [26,28] which would be expected to have important clinical implications for individuals with or without metabolic disease. Furthermore, a growing body of literature has examined both high intensity forms of interval exercise as it relates to glycemic control in patients with MetS and T2D. The purpose of the current review will be to synthesize findings from both modalities of high intensity interval training on markers of glycemic control in patients with MetS and T2D. The scientific evidence presented in the review will be useful for clinicians and other health-related professionals to formulate exercise-driven treatments for glycemic control.

2. High intensity interval training (HIIT)

High-intensity interval training (HIIT) is an exercise modality characterized by short bursts of vigorous activity interrupted by lower intensity or passive recovery periods [29–31]. The intensity of HIIT is often controlled by using a percentage of the maximal oxygen uptake (VO_{2\text{max}}), maximal heart rate (HR_{\text{max}}), maximal run velocity, peak power output (PPO) in watts (W) or ratings of perceived exertion (RPE) [32–38]. Currently, there is no established HIIT protocol, which has made it difficult to compare studies regarding volume, modality, and environmental conditions required to optimize benefits. Indeed, HIIT can be implemented by several types of exercise such as running, cycling, rowing, swimming and whole-body exercise [39–41]. The high-intensity bouts are generally performed to submaximal or near maximal capacity [42] (e.g. 80–95% HR_{max}, 85% PPO), or 90% maximal run
velocity \([25,32,34,35,42,43]\), and always interspersed with recovery periods (e.g., 25% PPO, 30% maximal run velocity, or 50% \(HR_{\text{max}}\)) \([32,34,35]\).

The duration of the bouts is highly variable as reported in the literature, however, 60 s bouts is the most common duration reported for high-intensity and recovery intervals \([34,35,44]\). In some studies, longer periods have been reported, such as 4 min of high-intensity intervals with 2 min recovery intervals \([30,45]\). The HIIT session generally start with a warm-up (4–5 min) at an intensity similar to recovery periods \([32]\). In general, the HIIT sessions consist of 4–8 bouts of high-intensity and recovery sessions typically lasting < 30 min \([46]\), with exceptions \([32]\) (Fig. 2A). In addition, HIIT subdivisions were reported in a recent review based on the work to interval ratio (work/bout) \([47]\). In detail, long-interval HIIT (LI-HIIT) is used for an interval training that includes 2–4 min of a high-bout at submaximal intensity. Moderate interval HIIT (MI-HIIT) is used for an interval training of 30–120 s of high-bouts. Short-interval HIIT (SI-HIIT) for training is used for training designed with < 30s of work/bout performed at sub-maximal intensity, and from 10 to 30 s of near maximal (all-out) intensity is used for SIT. Repeated sprint exercise (RST) is used for interval training that include bouts of \(< 10s\) at near to maximal intensity (all-out) (RST). The authors explained that when the HIIT protocol covers \(\geq 15\) min of work, it can be named as high-volume HIIT (HV-HIIT). Likewise, moderate-volume (MV-HIIT) is the name used for interval training consisting of 5–15 min of work, and low-volume (LV-HIIT) the interval training with \(\leq 5\) min of work. Finally, the length of training periodization also is used to classify HIIT; long-term HIIT (LT-HIIT) is used for protocol that includes \(\geq 12\) weeks, and short-term HIIT for protocols lasting \(\leq 4\) weeks (ST-

---

**Fig. 2.** Schematic overview of HIIT (A) and SIT (B) with the different parameters for their prescription (middle) and intensities (higher bouts above; lower bouts below). In addition, the different time sequence (up above) and exercise modalities (down below) at which both training protocols can be performed is also provided. VO\(_{2\text{max}}\): maximal oxygen uptake, RPE: Rating of perceiving exertion.
A. Jiménez-Maldonado, et al.

Table 1

Summary of studies that evaluated the effects of HIIT and SIT on glycemic markers in controls and individuals with MetS or T2D.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Subjects</th>
<th>Condition</th>
<th>Exercise training (duration, intensity, frequency)</th>
<th>Main results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alvarez et al. 2015</td>
<td>40 (40/0)</td>
<td>MetS</td>
<td>HIIT: 26 min (60 s at 70–100% HRmax: 120 s recovery). MT-HIT; LM-HIT; SI-HIT</td>
<td>HIIT reduced FPG, HOMA-IR. The same effects were observed with resistance training.</td>
</tr>
<tr>
<td>Alvarez et al. 2017</td>
<td>29 (16/12)</td>
<td>Children with IR</td>
<td>HIIT improved FPG, FI, OGTT, and HOMA-IR. HIIT increased muscle insulin signaling and Glut4 levels (protein) and this effect was not found in MICT. Moreover, HIIT improved the M-value of glucose, compared with continuous training. Additionally, HIIT reduced fasting insulin concentrations.</td>
<td>One single session of HIIT improved PPG 24 h after training. The effect was greater with internal training compared with continuous training.</td>
</tr>
<tr>
<td>Honkala et al. 2017</td>
<td>21 (13/8)</td>
<td>Prediabetes or T2D</td>
<td>HIIT: 4-10× (1 min at 90% HRmax; 1 min recovery) MT-HIT; MV-HIT; MI-HIT.</td>
<td>HIIT improved OGTT. The same effects were found with MICT. Exercise intervention improved HbA1c in participants.</td>
</tr>
<tr>
<td>Dela et al. 2018</td>
<td>25 (25/0)</td>
<td>T2D</td>
<td>HIIT: 8-12× (40 s to 60 s at 70–100% HRmax: 120 s recovery). MT-HIT; MV-HIT; MI-HIT(SIT).</td>
<td>HIIT increased muscle insulin signaling and Glut4 levels (protein) and this effect was not found in MICT. Moreover, HIIT improved the M-value of glucose, compared with continuous training. Additionally, HIIT reduced fasting insulin concentrations.</td>
</tr>
<tr>
<td>Reference</td>
<td>Subjects n</td>
<td>Condition</td>
<td>Exercise training, frequency, mode</td>
<td>Protocol</td>
</tr>
<tr>
<td>-----------</td>
<td>------------</td>
<td>-----------</td>
<td>-----------------------------------</td>
<td>----------</td>
</tr>
<tr>
<td>Little et al. 2011 [7]</td>
<td>6 (6/0)</td>
<td>T2D</td>
<td>2 weeks, 3 session/week, cycle ergometer</td>
<td>HITT</td>
</tr>
<tr>
<td>Mackensie et al. 2012 [19]</td>
<td>8 (8/0)</td>
<td>T2D</td>
<td>1 session in Hypoxia condition</td>
<td>HIIT</td>
</tr>
<tr>
<td>Magalhães et al. 2013 [1]</td>
<td>26 (26/0)</td>
<td>Healthy</td>
<td>16 weeks/3 sessions/week, cycling exercises</td>
<td>HIIT</td>
</tr>
<tr>
<td>Maixner et al. 2015 [48]</td>
<td>26 (9/17)</td>
<td>Healthy, obese, and obese with IR</td>
<td>26 weeks/3 session/week, cycle ergometer</td>
<td>HIIT</td>
</tr>
<tr>
<td>Little et al. 2016 [17]</td>
<td>7 (5/2)</td>
<td>T2D</td>
<td>12 weeks/3 sessions/week, treadmill exercises</td>
<td>HIIT</td>
</tr>
<tr>
<td>Ribeiro et al. 2016 [109]</td>
<td>47 (6/47)</td>
<td>MS</td>
<td>12 weeks (3-Sessions/running exercises)</td>
<td>HIIT</td>
</tr>
<tr>
<td>Ramos et al. 2016 [130]</td>
<td>37 (37/0)</td>
<td>MS</td>
<td>2 weeks (5 sessions/week, cycle ergometer)</td>
<td>HIIT</td>
</tr>
<tr>
<td>Marquis-Gravel et al. 2016 [113]</td>
<td>26 (9/17)</td>
<td>Healthy, obese, and obese with IR</td>
<td>26 weeks/3 session/week, cycle ergometer</td>
<td>HIIT</td>
</tr>
<tr>
<td>Mitranun et al. 2016 [122]</td>
<td>6 (6/0)</td>
<td>T2D</td>
<td>2 weeks, 3 session/week, cycle ergometer</td>
<td>HIIT</td>
</tr>
<tr>
<td>Madsen et al. 2015 [120]</td>
<td>23 (9/17)</td>
<td>Healthy, obese, and obese with IR</td>
<td>26 weeks/3 sessions/week, cycling exercises</td>
<td>HIIT</td>
</tr>
<tr>
<td>Ribeiro et al. 2017 [109]</td>
<td>47 (6/47)</td>
<td>MS</td>
<td>12 weeks (3-Sessions/running exercises)</td>
<td>HIIT</td>
</tr>
<tr>
<td>Maroto et al. 2018 [139]</td>
<td>56 (31/24)</td>
<td>Prediabetes patients</td>
<td>12 weeks (3-Sessions/running exercises)</td>
<td>HIIT</td>
</tr>
<tr>
<td>Robinson et al. 2017 [133]</td>
<td>38 (7/32)</td>
<td>T2D</td>
<td>16 weeks (64 sessions/cycle ergometer, walking)</td>
<td>HIIT</td>
</tr>
</tbody>
</table>

(continued on next page)
<table>
<thead>
<tr>
<th>Reference</th>
<th>Subjects n (M/F)</th>
<th>Condition</th>
<th>Exercise training (duration, frequency, mode)</th>
<th>Protocol</th>
<th>Classification of interval training (by Wen et al., 2019)</th>
<th>Main results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skleryk et al. 2013 [82]</td>
<td>16 (16/0)</td>
<td>MetS</td>
<td>2weeks/sprint in cycle ergometer</td>
<td>TER: 30 min at 60% VO\textsubscript{peak} SIT: 8 to 10 × (5 s “all-out” against a resistance of 0.05 kg/body mass: 80 s of rest)</td>
<td>ST-HIIT; LV-HIIT; RST</td>
<td>glycemic markers compared with the aerobic continuous training HIIT did not induce metabolic changes associated with insulin sensitivity and glucose uptake in skeletal muscle. The HOMA-IR was not modified by the exercise's protocol HIIT reduces the pro-inflammatory profile. Furthermore, HIIT reduced FPG and HbA1c levels. Interval training did not improve glucose parameters in all participants (HOMA index, HbA1c).</td>
</tr>
<tr>
<td>Steckling et al. 2016 [107]</td>
<td>17 (0/17)</td>
<td>MetS</td>
<td>12 weeks/3 sessions/week, running in treadmill</td>
<td>HIIT: 43 min (4 min at 90% HR\textsubscript{max}: 3 min at 70%HR\textsubscript{max})</td>
<td>MT-HIIT; HV-HIIT; LI-HIIT</td>
<td>Both types of exercise intervention lowered HbA1c.</td>
</tr>
<tr>
<td>Stensvold et al. 2010 [126]</td>
<td>43 (23/17)</td>
<td>MetS</td>
<td>12 weeks/3 sessions/week, treadmill walking or running</td>
<td>4 HIIT: 4 × (4 min at 85–95% HR\textsubscript{peak}: 3 min at 70% HR\textsubscript{peak}); Strength training: 50–40 min at 80–60% RM. Combined training HIIT-ST</td>
<td>MT-HIIT; HV-HIIT; LI-HIIT</td>
<td>Both types of exercise intervention lowered HbA1c.</td>
</tr>
<tr>
<td>Støa et al. 2017 [150]</td>
<td>38 (15/23)</td>
<td>T2D</td>
<td>12 weeks/3 sessions/week, running/walking exercises</td>
<td>HIIT: 4 × (4 min at 82% VO\textsubscript{2max}: 3 min at 82% VO\textsubscript{2max}). MICT: 56% VO\textsubscript{2max}</td>
<td>MT-HIIT; HV-HIIT; LI-HIIT</td>
<td>Both types of exercise intervention lowered HbA1c.</td>
</tr>
<tr>
<td>Tjønna et al. 2008 [80]</td>
<td>28 (13/15)</td>
<td>MetS</td>
<td>16 weeks/3 session/week, walking/uphill on treadmill</td>
<td>Control: without exercise MICT: 47 min at 70% HR\textsubscript{max} HIIT: 40 min (4 min at 90% HR\textsubscript{max}; 3 min active recovery at 70% HR\textsubscript{max})</td>
<td>MT-HIIT; MV-HIIT; MI-HIIT</td>
<td>HbA1c induced greater insulin sensitivity in muscle compared with MICT. In the same sense, interval training promoted better β-cell function than MICT.</td>
</tr>
<tr>
<td>Winding et al. 2018 [103]</td>
<td>32 (19/13)</td>
<td>T2D patients</td>
<td>11 weeks/3sessions/week, walking/cycling on treadmill</td>
<td>HIIT: 20 min (1 min at 95% PPO: 1 min at 40% PPO). MICT: 40 min at 50% PPO</td>
<td>MT-HIIT; MV-HIIT; MI-HIIT</td>
<td>HIIT reduced postprandial glucose and improved HOMA-IR and fasting glucose. The effects induced by HIIT were higher than MICT.</td>
</tr>
<tr>
<td>Wormgoor et al. 2018 [152]</td>
<td>22 (22/0)</td>
<td>T2D</td>
<td>12 weeks/3 sessions/week, cycling exercises, and resistance exercises</td>
<td>HIIT + Resistance training: 12 × (1 min at 95 PPO: 1 min recovery or 30 s at 125 PPO: 2:15 min recovery bouts). MICT + resistance training: 26 min at 55% PPO. Resistance exercise &gt; 2 sets of 12 repetitions at 75% RM</td>
<td>MT-HIIT; MV-HIIT; MI-HIIT or SIT</td>
<td>Both training protocols reduced HbA1c, however the effects of training disappeared after 6 months.</td>
</tr>
</tbody>
</table>

3. Sprint interval training (SIT)

Sprint interval training (SIT) is a category of interval training characterized by brief maximal or supramaximal exercise alternating with recovery periods that include passive recovery or light to moderate-intensity exercise. Exercise intervals are performed at ≥100% VO\textsubscript{2max}, PPO, maximal run velocity, or HR\textsubscript{max} and the recovery intervals include low-intensity exercise performed at 30–50 W, 10% PPO or passive recovery.

With SIT, the high-intensity bouts last ≤30 s with some using as little as 20 s, 15 s, or 5 s. The length of active recovery ranges from 1 to 4 min, with no established protocols at the time of this review. The most frequently used protocol is one with 30 s Wingate sprints interspersed with 4–6 recovery intervals at 4 min each.

In agreement with a recent classification, SIT also can be name repeated sprint training (RST) [47]. (Fig. 2B). In agreement with recent scientific evidence, during MetS and T2D, SIT improve insulin action primarily in skeletal muscle by reducing pro-inflammatory markers and increased blood flow, oxidative capacity and GLUT4 transporters (A). However, under the same conditions, the impact of interval training on insulin transport and insulin signaling in brain is unknown (B). On the other hand, evidence suggests that interval training does not modify insulin resistance in liver (assessed by HOMA-IR, and fasting insulin) during MetS and T2D (C). Considering that insulin action and glucose metabolism in liver contribute to de novo lipogenesis, it is possible that TGs generated from glucose are still affecting the brain (D). Conversely, experimental evidence indicates that HIIT and SIT reduced Hba1c during T2D and MetS and suggest that AGEs levels could be lower following interval training. Therefore, we predict that the damage induced by AGEs in BBB and brain following interval training could be attenuated or reverted (D). Finally, several studies demonstrate that HIIT reduced PPG in populations with MetS, and in T2D patients' acute hyperglycemia impairs cognitive function and deteriorate mood. The impact of acute hyperglycemia on brain function under MetS is unknown (E). Hence, studies are needed to identify the effects of acute hyperglycemia on the brain under MetS. These data could supplement the findings in regard to HIIT-induced attenuation of PPG in MetS. In contrast in patients with T2D acute hyperglycemia reduces brain function. Therefore, studies are required to elucidate the impact of interval training on PPG in T2D (E).
and insulin sensitivity index (SI) are obtained during the hyperinsulinemic-euglycemic clamp [64,65,67]. Although, hyperinsulinemic-euglycemic clamp using tracers show that glucose is disposed in numerous peripheral tissues, the greatest proportion originates from skeletal muscle [68]. The primary mechanisms responsible for regulating glucose uptake in skeletal muscle are glucose delivery, transport and metabolism [69]. Glucose delivery is mediated by blood flow in the muscle and the arterio-venous glucose difference [69–71]. Therefore, under conditions that increase capillarization in skeletal muscle, the available surface area will be wide, facilitating glucose delivery [69,70]. Glucose uptake occurs by facilitated diffusion through glucose transporter 4 (GLUT4) in skeletal muscle and adipose tissue [69,71]. Finally, hexokinase-mediated glucose phosphorylation is considered a key process in the regulation of glucose uptake in skeletal muscle [69,71]. In addition, some studies demonstrate that glycogen in skeletal muscle regulates glucose uptake in this tissue [72,73].

5. Effects of HIIT and SIT on insulin sensitivity

As was indicated in the Introduction section, the personal and economic burden of MetS and T2D in developed countries around the world highlight the need to innovative strategies to improve IS and glycemic control. In the section that follow, we will present an available evidence about the effects of interval training from studies using hyperinsulinemic-euglycemic clamp procedures and other markers of IS.

Karstoft and colleagues showed that participants with T2D who performed 80 sessions (walking exercises) of HIIT over 16 weeks had higher Ss values compared with MICT and sedentary groups [74]. The metabolic adaptation resulted from a reduction in body fat [74–76] and perhaps higher membrane-bound GLUT4 translocation [74]. In a similar fashion, Little et al. designed an exercise program consisting of 6 sessions of HIIT performed on a cycle ergometer in individuals with T2D, and a higher GLUT4 expression and mitochondrial activity in skeletal muscle following short-term training [77]. In contrast, cycle ergometry using one leg showed that 8 sessions of HIIT completed over 2 weeks increased glucose uptake in skeletal muscle without an increase in GLUT4 expression, insulin signaling intermediates or mitochondrial content in T2D patients [78]. Increased glucose disposal was attributed to improve skeletal muscle blood flow leading to enhanced glucose delivery [78]. The effects of short-term SIT on IS in T2D patients has also been examined [79]. Six sessions of SIT (Wingate), performed over 2 weeks, was a sufficient stimulus to improve Ss. In fact, the M value for the clamp was higher following SIT and similar to a MICT group, despite the MICT group performing on average 50% longer duration of exercise [79]. Unfortunately, the molecular adaptations induced by training to increase Ss were not reported.

The impact of HIIT on IS in individuals with MetS has also been evaluated [80]. A training study consisting of 48 sessions of HIIT performed with walking/running exercises on a treadmill increased insulin receptor phosphorylation at threonine 612 in the vastus lateralis muscle and adipose tissue [80]. Similarly, 24 sessions of SIT performed on a cycle-ergometer increased insulin receptor phosphorylation at threonine 612 and Akt phosphorylation at serine 473 (both indicating improvements in insulin signaling) in skeletal muscle in obese participants with IR [45]. The improvements in insulin signaling were explained by improved oxidative capacity in the skeletal muscle [45]. It is worth noting that the molecular adaptations induced by long-term HIIT in humans were also observed db/db mice which possessed mutation in the long form of the leptin receptor. In this study, 50 sessions of HIIT performed over 10 weeks increased GLUT4 protein content and insulin signaling in skeletal muscle [81]. These findings illustrate the robust and independent effects of HIIT to overcome the well-known constellation of metabolic derangement of this mouse model.

With respect to the efficacy of the short-term SIT programs to improve the glycemic control in MetS patients, it was reported that 6 sessions of SIT (cycling exercise) performed over 2 weeks, did not modify insulin signaling (GLUT4 protein or AS160 phosphorylation levels) in skeletal muscle [82]. Taken together, these findings suggest that long-term interval training can improve insulin signaling and increased expression of GLUT4 in skeletal muscle in patients with MetS and T2D, whereas short-term interval training seems be less effective at improving insulin signaling in the skeletal muscle during MetS.

6. Effects of HIIT and SIT on markers of insulin resistance

Insulin resistance (IR) is a condition where the biological action of insulin is reduced in peripheral target tissues [63,83]. IR produces a disproportionate insulin concentration to the level of glycaemia [63]. Therefore, IR is associated with a hyperinsulinemic state [63,83–85]. A reduction in intrinsic tyrosine kinase activity of the insulin receptor is considered the primary mechanism responsible for IR [86,87]. Reductions in tyrosine kinase activity can be induced by the pro-inflammatory cytokines such as TNF-α and IL-6 [86,88–95]. In addition, lipids such as ceramides also reduce tyrosine activity of the insulin receptor and Akt protein expression [96,97]. Moreover, hyperinsulinemia induce IR [83,87] through insulin receptor desensitization [83,84,87]. In the following section, we will review the effects of interval training on markers associated to IR in individuals with T2D and MetS.

6.1. Fasting insulin concentrations

Fasting insulin (FI) concentrations have a strong relationship with IR [83,98]. In fact, elevated FI is considered an independent predictor in the development of MetS [99]. However, to date, there is not an established FI concentration considered for diagnosis of MetS. Some authors suggest values > 9.0 μU/ml as the cut-off for prediabetes [100], while others reported 7.35 μU/ml as a cut-off value for MetS [101]. In participants with T2D, FI concentrations were significantly lower after long-term HIIT performed with walking exercise [74]. In opposition to HIIT, FI concentrations were not different following MICT [74]. Based on these results, the authors suggested that lower FI resulted from adaptations in glucose disposal (i.e., improved insulin signaling in skeletal muscle) more so than an effect on pancreatic β-cell insulin secretion [74]. The same group also reported that after a single session of HIIT, FI was lower compared to a non-exercise control, but similar to continuous training [102]. The authors showed that both training modalities similarly improved insulin-dependent and independent glucose uptake, and that the energy intake in the participants of the HIIT group was lower compared with control and MICT. In agreement with authors, the behavioral responses leading to reduced energy intake likely contribute to lower FI following HIIT [102]. These findings are intriguing and highlight the need to future studies to examine further if HIIT reduce effect on appetite that contribute to the superior effect of HIIT on FI compared to MICT. On the other hand, another study reported that 33 sessions of cyclergometry HIIT did not change FI in patients with T2D [103]. Since the studies described above had different length and were performed employing different exercise modalities (treadmill running, walking and cycling exercises), it is not possible to establish a biochemical effect of HIIT on FI in patients with T2D. Future studies with similar duration (session numbers) will be needed to examine whether disparities exist in the response to different modalities of exercise as it relates to the benefits of HIIT on FI concentrations in T2D patients.

In a similar fashion, the effects of SIT on FI concentrations are controversial. Specifically, one study reported that 24 sessions of SIT performed on a cycle ergometer did not modify FI levels in participants with T2D [104]. Similar results were observed following 12 sessions of Wingate SIT [105]. In contrast, 30 sessions of SIT induced a significant reduction in FI concentrations in patients with T2D [106]. The intensity of SIT in the Banitalebi et al. study [106] was more strenuous than the reported by Ruffino et al. [104]. These findings suggest that the intensity of SIT performed on cycle ergometers, and less likely the length
of training, is a critical factor for eliciting reductions in FI in T2D patients. Further studies are warranted to evaluate differences between run and cycle ergometer-based long-term SIT with regards to the effects on FI during T2D.

Studies have examined the effects of HIIT on FI in patients with MetS; however, the findings are equivocal. Long- (e.g., 36 sessions) and short-term (e.g., 10 sessions) HIIT performed on a treadmill and cycle ergometer, respectively, did not modify FI [107,108]. Others have shown that long-term HIIT (i.e., 30–48 sessions) on a cycle ergometer reduced FI in patients with MetS [109–111]. Moreover, participants showed reductions in fasting glucose levels and anthropometric variables associated with obesity (fat mass, waist circumference, triceps skinfold) [126–128]. The differences in results were likely attributed to a number of confounding variables such as body composition [75].

The impact of cycle ergometer-based SIT (long- and short-term) on FI in MetS individuals has also been evaluated [82,112,113]. First, six sessions of SIT did not significantly change FI [82]. In agreement with short-term protocols, Gillen et al. did not find effects on FI after a long-term (36 sessions) SIT intervention [113]. In both studies, blood glucose and free fatty acid concentrations were not modified. Therefore, it is possible that both molecules were still working on β-cells to stimulate insulin secretion [114]. However, a more recent study reported lower FI concentrations following 18 SIT sessions with increased VO2max [112]. Since VO2max is negatively associated with chronic inflammation [115], it is possible that lower chronic inflammation could be present in the participants and that might explain an improved FI.

6.2. Fasting plasma glucose

A fasting plasma glucose (FPG) concentration > 126 mg/dl (7.0 mmol/l) is one of the criteria for diagnosis of T2D [9,116]. IR in liver is the primary mechanism responsible for impaired fasting glucose by impairing the biological capacity of insulin to inhibit glucose production and secretion. In the current section will focus on the impact of HIIT and SIT on FPG during T2D and MetS.

Although exception exist [117], HIIT consistently decreases FPG in patients with T2D [103,118–122]. Specifically, Winding et al. [103] conducted 33 sessions of cycle-ergometer HIIT and found lower FPG. Similar results were observed with the MICT group that were required to perform ~45% more time than the HIIT protocol [103]. These results emphasize the efficiency of HIIT to produce comparable effects on FPG as MICT. In line with the previous report, other studies showed that 48 sessions of HIIT (jogging/running) over 16 weeks reduced FPG in adults with T2D [118]. Finally, 36 sessions of running treadmill or elliptical HIIT over 12 weeks were effective at reducing FPG and improving VO2max [119,122]. Conversely, one study reported 32 sessions of HIIT performed on a cycle ergometer did not modify FPG in T2D older adults [117]. Despite the lack effect on FPG on the later, the majority of these studies suggest that HIIT is an effective strategy to decrease FPG concentrations during T2D.

Compared with HIIT, fewer studies have examined the effects of SIT on FPG in patients with T2D [104,106]. One study reported that 40 sessions of cycle-ergometer SIT performed over 8 weeks did not modify FPG [104]. Others have shown that a longer training period (i.e., 10 weeks) with fewer sessions (i.e., 30) reduced FPG [106]. Additional studies are required to determine to develop a more thorough understanding of HIIT on FPG. In addition to the studies focused on the effects of interval training on FPG in T2D patients, others have reported the impact of HIIT and SIT on FPG during MetS [80,107,113,123–126]. While some authors reported improvements in FPG following treadmill running HIIT [80,107], others did not find significant effects of interval training on FPG with cycling [140–142] and treadmill exercises [143]. At this time it is difficult to untangle the reason for disparate findings among the studies conducted in patients with MetS.

Similar to HIIT, the impact SIT on FPG in MetS also has been evaluated. One group reported that 36 sessions performed during 12 weeks on a cycle ergometer did not modify FPG [113]. However, the same protocol improved IS and induced higher mitochondrial activity in skeletal muscle [113]. Others showed that 6 sessions of SIT performed with cycling exercise was not an effective strategy to reduce FPG with MetS [82]. These studies in patients with T2D and MetS suggest that interval training may not induce changes in liver leading to improvements in IS.

6.3. HOMA

The homeostasis model assessment (HOMA) is a practical index used to evaluate the interaction between glucose and insulin dynamics [65,127]. HOMA-IR is a mathematical model that evaluates systemic insulin resistance (HOMA-IR) and HOMA-%β evaluates pancreatic β-cell function [127]. Both models have a strong relationship with the euglycemic clamp method for healthy and T2D populations [127,128]. First described by Matthews et al. [157], HOMA-IR is calculated as [Fasting Insulin (μg/ml)]*[Fasting Glucose (mmol/l)]/22.5, and HOMA-%β is calculated as 20*FI (pg/ml)/[FG (mmol/l)] - 3.5. HOMA-IR values between 0.5 and 1.4 are considered normal, ≥1.9 are indicative of early IR, and ≥2.9 indicate IR [83,128,129]. A reduction in β-cell function is highly correlated with IR [129]. The β-cell function > 110% is considered normal and <80% is considered low β-cell function [157]. The following section will focus on current state of knowledge on the effects of HIIT and SIT on HOMA-IR and -%β in MetS and T2D.

An extensive body of evidence supports improvements in HOMA-IR and HOMA-%β in morbidly obese participants [103,107,109–111,120,124,130–135]. Fewer studies have been conducted examining the acute or chronic effects of HIIT in patients with T2D and MetS. Mackenzie et al. [136] evaluated the acute effects of cycle ergometer HIIT in T2D with 5.5 active/recovery intervals at 120% lactate threshold. HOMA-IR and HOMA-%β improved immediately after HIIT. Moreover, the beneficial effects of HIIT on HOMA-IR and β% effects were maintained 24 h following the exercise bout performed on a cycle ergometer [136]. The molecular approach explaining that acute HIIT altered both indexes was a greater GLUT4 translocation, and post-exercise glycogen depletion and vasodilator function. In contrast, the impact of long-term HIIT on HOMA-IR are inconclusive. In fact, one study reported that 33 sessions of cycle ergometer HIIT decreased HOMA-IR [103]; the lower glycemic index after the interval training resulted from an improved hepatic insulin sensitivity [120]. Another study used 36 HIIT sessions and did change HOMA-IR [133]. However, improved body composition and VO2max were reported following HIIT [164]. At this time, we are unaware of reports examining the effects of SIT on HOMA-IR or –%β in patients with T2D.

Likewise, there are several studies focused to assess the impact of interval training on the HOMA index with MetS [82,107–113,124,130–132,135]. Most studies demonstrate that long-term HIIT performed with cycling exercise is an effective strategy to improve HOMA-IR [109,111,130] by increasing oxidative capacity in muscle tissue [111,124,125,130]. Others show that 36 to 48 HIIT sessions performed on a treadmill reduced HOMA-IR, to a greater extent than MICT, mainly in participants with high HOMA-IR [134]. However, studies using a lower number of HIIT sessions (10 to 18) with cycling exercises [108,137] did not find changes in HOMA-IR and HOMA-%β. The lack of body composition changes could explain partially the null effects of interval training on HOMA-IR [75,108]. Moreover, these data suggest a dose-response relationship between HOMA-IR and the number of HIIT sessions completed in patients with MetS. In opposition to HIIT, mixed results were reported for SIT interventions in patients with MetS. For instance, outdoor run SIT and jump rope [138] reduced HOMA-IR in adolescents; however, cycle ergometer-based (Wingate) SIT did not improve HOMA-IR in young adults [113]. These findings suggest that the exercise modality and age are among the mediators of the changes in the HOMA index after SIT during MetS.

The amount of...
skeletal muscle mass required to perform running and jumping exercises compared to cycling can be a relevant factor to induce changes on HOMA-IR. It would be expected that the increased muscle mass used during SIT would result in a greater improvement in HOMA-IR in individuals with MetS. Moreover, evidence suggests that training intensity is also related to decreases in HOMA-IR; indeed, HOMA-IR was decreased following 18 SIT sessions performed to supramaximal intensity (125% VO$_{2\text{max}}$), but not at 100% VO$_{2\text{max}}$ [112].

### 6.4. Impaired glucose tolerance

Glucose tolerance is defined as the capacity for glucose uptake in peripheral tissues over a pre-determined period of time [139]. It is typically measured via the oral glucose tolerance test (OGTT), and is often used as a standard for screening and diagnosis of gestational diabetes, T2D, and MetS [140,141]. Blood glucose concentration is measured immediately prior to a 75 g of solution of glucose followed by blood sampling again at 2 h [79]. Glucose concentrations are considered normal below 140 mg/dL and impaired glucose tolerance (IGT) is defined as glucose concentration at 140–199 mg/dL [7.8–11.0 mmol/l]. Blood glucose concentrations ≥ 200 mg/dL (11.0 mmol/l) represent criteria for diagnosis of diabetes [9]. Elevated responses during OGTT typically indicate IR in skeletal muscle more than other tissues such as liver [142]. Moreover, OGTT estimates the capacity of β-cells to release insulin under a glucose load during the first 60 min of the test [63]. In the following section, we will describe the effects of HIIT and SIT on OGTT in individuals with T2D or MetS.

The majority of the studies conducted to date demonstrate that HIIT improves glucose tolerance in patients with T2D. In one study, 8 weeks (24 sessions) of HIIT using cycle ergometry improved glucose tolerance, HOMA-IR and HOMA-8% suggesting a better β-cell function and the attenuation of IR in muscle [120]. In a similar fashion, 12 weeks of cyclogrammetry-based HIIT (48 sessions) reduced glucose concentration during OGTT. Although similar results were observed in the MICT group, this finding highlight the powerful effects of HIIT and the practical benefits associated with lower time commitment over traditional MICT [143]. The authors suggested that the improvement in glucose tolerance observed in participants with T2D was the consequence of a higher skeletal muscle glucose uptake [143]. Exceptions to these findings exist with one study showing that 11 weeks of HIIT performed with cyclogrammetry did not improve glucose tolerance in older T2D patients [103].

The effects of SIT on glucose tolerance in participants with MetS have not been thoroughly examined. To date, Fisher and colleagues [137] have been the only group who evaluate glucose tolerance following 6 weeks of SIT versus MICT in sedentary middle-aged obese males with characteristics of MetS. Similar improvements in glucose tolerance were observed when comparing the SIT with MICT responses [137]. Lower body fat mass was observed for both groups, which highlights the needs for future studies to differentiate the effects of fat loss vs the independent effects of exercise on glucose tolerance [75].

### 7. Effects of HIIT and SIT on other markers of glycemic control

#### 7.1. Glycated hemoglobin

Glycated hemoglobin (HbA1c) is a biochemical parameter used to examine long-term glycemic control [98,144–146]. HbA1c concentration is reported as a proportion of total hemoglobin isoform A (HbA) [20], and values > 5.7% to 6.4% are considered as high risk for diabetes, and values ≥ 6.5% are used to diagnose diabetes [9]. Values ≥ 6.5% are also good predictors of cardiovascular disease, microvascular complications and all-cause mortality [145,147,148]. Furthermore, increases in HbA1c are associated with lower mitochondrial activity and skeletal muscle of individuals with T2D following aerobic exercise [149].

Recent studies have evaluated the effects of HIIT and SIT on HbA1c during T2D and MetS [81,103,117–120,122,123,143,150–152]. HIIT performed with cyclogrammetry decreased HbA1c in patients with T2D [103,117]. Although the authors did not elucidate the molecular mechanism induced by HIIT responsible for reducing the HbA1c, the authors suggested a strong correlation between the reduction of both visceral fat and HbA1c [117]. Additional studies using running at the modality of HIIT show similar capacity to reduce HbA1c in participants with T2D [122,151,152]. In the studies described above, the changes in HbA1c were associated with increased aerobic capacity (i.e., VO$_{2\text{max}}$) [103,122,151]. Since it is well known that increased VO$_{2\text{max}}$ with exercise training is, at least in part, associated with enhanced oxidative capacity and mitochondrial mass in skeletal muscle [151,153,154], it is possible that lower HbA1c results from higher mitochondrial activity in skeletal muscle.

In contrast to HIIT, there are fewer studies that have evaluated the impact of SIT on HbA1c in T2D participants [79,150]. One study showed that cycle ergometry SIT combined with resistance training reduced HbA1c and improved VO$_{2\text{max}}$ [150]. Although the authors did not explain the molecular and physiological adaptations for the reduced HbA1c concentrations, it is possible that there was a direct association and effect between HbA1c changes and VO$_{2\text{max}}$ possibly increasing the mitochondrial activity and the glucose uptake in skeletal muscle. Although the conclusion of resistance training in the study design limits the interpretation of these data as it is related to the effect of SIT on HbA1c concentration, evidence has emerged that short-term (6 sessions over 2 weeks) SIT reduced the HbA1c in participants with T2D and prediabetes [79]. Nevertheless, the molecular mechanism responsible for lower HbA1c levels following interval training was not reported [79]. Current scientific evidence suggests that short and long-term interval training improves HbA1c in T2D patients.

Finally, the impact of HIIT on HbA1c levels in population with MetS also has been studied [81,107,143]. In particular, HbA1c was lower after long-term HIIT performed with running exercise on a treadmill [107] or cycle ergometry [143]. In a study by Steckling and colleagues [107], lower HbA1c after HIIT was associated with anti-inflammatory effects. These findings suggest that HIIT may decrease peripheral inflammation which has been shown to induce metabolic disorders associated with MetS [107]. Similarly, Safarimosavi et al. reported that HIIT was the best stimulus to reduce HbA1c compared with several modalities of continuous training [143]. The authors indicated that during interval training, the metabolic stress is higher than MICT, and HIIT enhances the activity of proteins associated with glucose uptake (i.e. AMPK, CaMKII, and PGC1-α) that increase insulin sensitivity and improve glycemic markers such as HbA1c. Furthermore, this study provides evidence that exercise intensity is key to lowering HbA1c concentrations. These findings have been corroborated in a meta-analysis [19]. Accordingly to the available information, the HIIT is an efficient strategy to improve the HbA1c during the MetS.

#### 7.2. Postprandial glucose

Postprandial glucose (PPG) refers to blood glucose concentrations following a meal or test meal in laboratory settings [155]. The magnitude of PPG is primarily determined by the effects of food ingestion on insulin secretion and peripheral insulin sensitivity [155]. Numerous studies have identified a strong relationship between PPG and CVD in patients with T2D [155–157]. The continuous glucose monitoring (CGM) system is the most widely employed method used to evaluate PPG [77,123,158]. The CGM is performed with an abdominal subcutaneous sensor connected to a CGM monitor [123,159]. Interstitial blood glucose concentrations are averaged at 5 min intervals [159]. PPG is reported as peak, mean and area under the curve (AUC) for 2 h following a meal [123].

Recent studies have evaluated the impact of HIIT on PPG in those with T2D, pre-diabetes and MetS [74,77,103,123,159]. Little et al. [77]...
reported that 6 sessions of HIIT performed over 2 weeks with a cycle-ergometer reduced hyperglycemia (CGM during 24 h, and 2h PPG) in older adults with T2D. The authors reported that the improvement in glycemic control after HIIT resulted from higher oxidative capacity and a GLUT4 expression in skeletal muscle [77]. In contrast, Rafiei et al. [140] used 10 sessions of cycle-ergometer HIIT over two weeks and did not find an effect on PPG in patients at risk of T2D. However, the same intervention improved glucose variability (i.e., blood glucose fluctuations that occur throughout the day) [123]. Finally, others reported that a single cycling exercise HIIT session significantly improved PPG in individuals with obesity [159]. The authors reported a greater effect on PPG with HIIT compared with MICT despite lower exercise volume. In agreement with the authors, a higher post-HIIT metabolic rate could be a physiological adaptation responsible for reducing PPG [178], and may be related to higher rates of glycogen utilization that accompanies HIIT compared to MICT. To the best of our knowledge, no studies have examined the effect of SIT on PPG during T2D and MetS. Therefore is also scant scientific literature available about PPG and HIIT; thus, it is impossible to draw firm conclusions about the effects of interval training on PPG during T2D and MetS. Further studies are needed to characterize the physiological and metabolic adaptations induced by HIIT and SIT to improve PPG.

8. Conclusions and remarks

The incidence of MetS and T2D has increased around the world leading to extensive personal and economic burden. The pathophysiology present during MetS and T2D lead to secondary complications (e.g., neuroinflammation, BBB leakage, brain atrophy, neural connection disruption, retinopathy, nephropathy, neuropathy, cardiovascular disease and poor wound healing). The ADA (2011) recommends a minimum of 150 min/week of moderate-intensity PA such as walking or 75 min/week of vigorous-intensity PA for individuals with MetS or T2D [9]. However, lack of time is the most often reported barrier to achieve these recommendations. By its very nature, HIIT and SIT have the potential to attenuate or even eliminate the barriers for time. Overall, the available literature reveals that both HIIT and SIT training (performing running exercises) produce beneficial effects on S_{I} as determined by hyperinsulinemic-euglycemic clamp or markers of IR such as glucose tolerance and HOMA index (Table 1). These findings are associated with improvements in whole body S_{I} as a consequence of increased blood flow, oxidative capacity, and GLUT 4 expression in skeletal muscle. In contrast, findings about interval training on FI, and FPG, are not concordant. This suggests that the liver is less prone to recover the functions that occur throughout the day) [123]. Finally, others reported that the liver is less prone to recover the insulin sensitivity of brain networks in subjects with type 2 diabetes, PLoS One 11 (2016) 1-94, doc#https://doi.org/10.1371/journal.pone.0147268.

References


68. R.A. Defronzo, J. Jacot, E. Jequier, E. Maeder, J. Wahren, J.P. Felber, The e


72. R.S. Metcalfe, J.A. Babraj, S.G. Fawkner, R.M. Wilson, Induced fasting insulin pre-

73. K.C.C. Sung, M.H.H. Seo, E.J.J. Rhee, A.M. Wilson, Elevated fasting insulin pre-


77. S.P. Mortensen, The e

78. K. Karstoft, C.S. Christensen, B.K. Pedersen, T.P.J. Solomon, The acute e

79. K. Karstoft, K. Christensen, B.K. Pedersen, T.P.J. Solomon, The acute e


Continuous vs interval training improves glycaemic control and pancreatic β-cell function from measurements in the fasting state and during an oral randomised trial, Int. J. Cardiol. 245 (2017) 245


