Review Article

High-Intensity Interval Training: A New Fashion for An Old Suit for Patients with Chronic Diseases

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Abstract

High-intensity interval training (HIIT) has been established as a credible exercise program for patients with chronic diseases. HIIT plays a role in the individual’s physical conditioning, body fat control and glycemic levels to a similar, or even superior effect, compared with moderate-intensity continuous training (MICT). However, little is known if such benefits are applied to patients with chronic diseases. The aim of the present review was to analyze the recent findings on the effects of HIIT on safety, efficacy, and adherence for patients with coronary artery disease (CAD) and heart failure (HF), cancer and type 2 diabetes. The pooled information highlighted the efficacy of HIIT protocols to improve cardiorespiratory fitness to a similar extent than MICT, within a shorter time as an advantage. Despite the lack of agreement to prescribe HIIT, recent data has encouraged the application of HIIT in patients with chronic diseases, but its safety, efficacy, and viability need further studies to ensure this practice in the clinic.

Keywords: exercise, high-intensity interval training, moderate intensity continuous training, cancer, cardiovascular, type 2 Diabetes

Introduction

Physical inactivity is an urgent public health concern. According to a global physical activity survey 31% of adult’s population and 78% of adolescents are inactive, accounting for five million deaths annually [1,2]. Are considered inactive who do not reach the minimum physical activity recommendations weekly. To date, international agencies [3,4] recommend 150 mins of moderate, or 75 mins of vigorous, aerobic physical activity weekly. The minimum physical activity also incorporates 2-3 resistance exercise sessions for large muscle groups and stretching sessions [5].

A growing body of evidence demonstrated the inverse relationship between the highest level of physical activity and the incidence/mortality of chronic diseases. An observational, prospective and multicenter study showed that individuals who achieved 27-30 METs (Metabolic Equivalents), approximately 3 times the guidelines recommendations were at lower risk of 13 types of tumors. From these, 7 types of tumors (esophageal adenocarcinoma, liver, stomach, colon, endometrium, kidney and leukemia Myeloid) presented greater than 20% risk reduction [6]. This was the largest cohort showing that levels of activity may be necessary to achieve greater benefits against the incidence of cancer.
In cardiovascular diseases or in diabetes, the inverse correlation between greater levels of physical activity with events is well established [7,8]. Since the classic work of Morris et al. [9] it has been known that sedentary jobs presented a higher incidence of coronary diseases than more active jobs partner. Moreover, active workers tended to present lower rates of mortality. Morris’s works were the first epidemiology evidence suggesting that sedentary lifestyle is a silent weapon. His contribution to the exercise science in the last century is undeniable and stimulates several groups of researchers to understand how to avoid physical inactivity and, at the same time, to prescribe effective exercise protocols.

Effective exercise should be interpreted according to the FITT principle. This acronym means Frequency, Intensity, Time and Type. The four components of the FITT principle are the basics to deliver an effective and personalized exercise protocol. However, just a few studies clarify these principles in their protocols which turns difficult to interpret the outcomes and further reproduce it. Out of potential exercise protocols in the clinical practice, the HIIT (high-intensity interval training) has gained attention as a viable alternative to the MICT (Moderate-Intensity Continuous Training). Recent research shows that the cardiovascular adaptations that occur with HIIT are similar and in some cases superior to those that occur with MICT [10]. In other words, the same benefits in shorter time. The “HIIT topic” remains very popular among exercise enthusiasts and achieved the third position in the last ACSM fitness trends in 2019 [11]. However, the growth of popularity has not been supported by the growth of high-quality scientific evidence.

One recent review study considered the efficacy of HIIT to augment the functional capacity of individuals with cardiovascular, pulmonary, and diabetes diseases [12]. For patients with cardio or pulmonary diseases, HIIT protocols was as effective as traditional MICT, improving functional capacity and quality of life. In diabetes, studies with HIIT reported benefits in improving insulin resistance, cardiorespiratory system, and BMI control what suggesting similar effects of either HIIT or MICT improving peak power output and reducing body fat. However, the lack of safety concerns and the limited number of observations stimulate novel researches focusing on feasibility, safety and efficacy of HIIT protocols for patients with cardiovascular and type 2 diabetes. This review included cancer studies as a potential eligible disease to consider HIIT in their complex clinical management. Despite the growing popularity, the majority of HIIT studies has been conducted with healthy young men and women; whereas the rationale to consider HIIT protocols in patients with chronic diseases is uncertain [13].

This review aimed to discuss the potential efficacy and safety as well as the advantages and disadvantages of HIIT in patients carrying chronic diseases including cardiovascular, cancer and diabetes.

Definitions and historical perspective

The basics of HIIT protocols incorporate a burst of cycles of exercise interspersed with recovery periods. HIIT protocols follow the FITT principles, and also incorporate an important variable, the rest of intervals. Bouts of exercise and recovery in the HIIT may vary in intensity and time. The exercise intensity likely achieves 85% to 95% of maximal oxygen consumption (VO₂max), and recovery being passive (no active movement) or using active with patterns of movements from 50% to 70% of VO₂max [14,15]. VO₂max is the gold-standard metabolic unit for exercise prescription. VO₂max is interpreting as the body’s upper limit for using and distributing oxygen for energy production, also known as the maximal aerobic capacity [16]. One variation of HIIT protocol is the SIT (Sprint Interval Training) which incorporates very short bouts at intensity beyond VO₂max (15-30 sec) with long recovery intervals (2-4 min) [17]. Although evidence of SIT protocol is emerging in patients with chronic diseases (i.e. Type 2 diabetes), this review aimed to focus on HIIT protocols.

The HIIT is not exactly a new idea. During the 20ths and 30ths, the long distance runner Pavoo Nurmi integrated interval training in his workouts. He included sprints of 400 m during 10 km or 20 km sessions. After World War II,
the concept of interval training became very popular among European athletes. One was Emil Zatopek who included sprints running within 3 km and 10 km distance [18]. In the 60ths, it was published the first study comparing two different protocols of interval training [19]. Choosing long intervals (2-3 min) resulted in better results in cardiopulmonary metabolism. They also noted that these benefits did not only affect athletes, but also accelerated rehabilitation of patients in the recovery period. Certainly, famous athletes played a role in the popularity of HIIT and motivate novel studies in participants with chronic diseases.

**Physiological adaptations to HIIT**

The energy required to sustain the demands of exercising muscles come for at least three major metabolic systems. One, faster and limited, originates from storage ATP and ATP-CP, and no taking longer 30 sec of maximal effort. Two, the anaerobic glycolysis, is preferred for a limited period of time (usually until 2 min of maximal effort), but stay present even in longer bouts. Third, the aerobic glycolysis, also known as oxidative metabolism, this energy pathway produces ATP through the breakdown of carbohydrates and fat in the mitochondria [20]. The manipulation of intensity and duration of exercise specifically modifies intracellular signalling and protein synthesis rates at the cellular and total muscle levels.

The utilization of specific metabolic or ventilatory responses to incremental cardiopulmonary exercise test (CPET) is shown to be superior to more generic prescriptions, such as those that proxy of percentages of maximal heart rate or maximal oxygen consumption (%VO₂max). More specifically, the utilization of blood lactate or ventilatory responses to incremental exercise can identify unique training zones that anchor different intensities of training to the two lactate or ventilatory thresholds (LTs or VTs, respectively) and VO₂max for each individual independent of disease severity or baseline fitness [21]. The role of each energetic pathway is not linear and they tend to work simultaneously (Figures 1A & 1B). Some exercise principles, such as intensity, time and the rest interval, will determine the predominance source of energy. For instance, endurance continuous sessions of 60 sec at high intensity (>80% VO₂max), the proportional of aerobic metabolism over anaerobic glycolysis is 70%/30%, respectively [22]. This metabolic predominance tends to be quite different in the HIIT protocol, where the rest interval assumes a crucial role. To date, researchers have focused on three leading metabolic adaptations following HIIT protocols and compared with MICT training.
Improving cardiovascular fitness and VO_{2} max are major goals of cardiac rehabilitation programs. Recent studies show that the cardiovascular adaptations that occur with HIIT are similar, and in some cases superior, to those that occur with MICT, within shorter time [10,16]. One major difference between protocols is that HIIT enables a greater amount of work by alternating high-intensity exercise with lower-intensity or rest intervals. The principles of HIIT training, for example, time of exercise bout versus time of rest, can elicit diverse achievements in cardiovascular parameters [23]. One systematic review and meta-analysis included 28 studies of HIIT and MICT to investigate the effects on maximal oxygen consumption in health middle-aged adults. Both, HIIT and MICT elicited improvements on VO_{2} max compared to no-exercise controls. There small beneficial effect of HIIT over MICT, and interventions of long duration were critical in both protocols to achieve additional benefits on oxygen consumption [24]. These data indicated that the binomial time effort and time of recovery are relevant to the final outcomes. A meta-analysis review which indicated no difference between HIIT protocols and MICT for VO_{2} improvements, yet greater improvements in VO_{2}max following HIIT occurred in healthy young individuals [25]. Thus, great divergences among protocols may partly explain the mixed results on VO_{2} improvements.

In parallel to cardiovascular adaptations, skeletal muscle metabolism is critically influenced by the HIIT. Augments in size and number of mitochondria are becoming a hallmark of HIIT adaptation on skeletal muscle cells [26]. Until recently, mitochondrial density was a physiological adaptation only linked with MICT programs. The observation that mitochondrial dysfunction is a functional driver in chronic diseases, including carcinogenesis, diabetes and cancer-associated cachexia, the potential role of HIIT to increase mitochondrial density is promising.

HIIT sessions can elicit physiological adaptations that mirror continuous endurance training. As such, one bout of HIIT can phosphorylate central enzymes (AMPK, p38 MAPK, and PGC-1alpha) leading to mitochondrial biogenesis [17,27]. However, there are some singularities on the molecular cascade of mitochondrial biogenesis following HIIT protocols. Some authors suggest that the pathway of activation of peroxisome proliferator-activated receptor-g coactivator-1α (PGC-1α), a master regulator of energy in the cell, differed consecutive of HIIT protocol from regular MICT [28,29]. While HIIT protocols operate for phosphorylation of adenosine monophosphate-activated protein kinase (AMPK), the MICT tended to phosphorylates calcium–calmodulin kinase (CaMK) [27,30]. AMPK phosphorylation is sensitive to exercise volume and intensity. For example, brief bouts of maximal exercise, intermittent or continuous setting, but no longer than 10min, evoked similar cascades signaling of mitochondrial biogenesis. Yet, data showed no skeletal muscle mitochondrial adaptations following 6 weeks moderate continuous protocols [16].

In parallel to higher mitochondrial density and function, a shift favoring fat acid oxidation has been documented after HIIT sessions [31–33]. Indeed, the higher mitochondrial capacity after HIIT was connected with greater capacity for fatty acid oxidation with interval training [34]. However, compared with cardiovascular adaptations, the evidence of fat oxidations as the main fuel source after interval training is narrow. Traditionally, fat acid oxidation has been consistently demonstrated in response to moderate intensity continuous exercise training. An extensive review study of the relationship between fat oxidation and interval training was recently published [35]. The authors observed that interval training increase fatty acid oxidation only in 50% of studies, with more favorite results with HIIT protocols than SIT. Therefore, preliminary evidence suggests larger increments of fat burning occurred with greater duration or volume of HIIT, which trend to approximate of MICT protocols. Overall, the authors highlighted the great variability among interval training protocols, the lack of non-exercise control group, and the intrinsic day-to-day variation of fat oxidation are major challenges for future investigations debate on this topic.

Based on the specific physiologic adaptations on cardiovascular and skeletal muscle metabolism following interval training, which may suppress the moderate continuous training with shorter exposure time, we carried out a review of
safety and efficacy of HIIT versus traditional moderate continuous training in patients with cardiovascular disease, cancer, and diabetes.

**HIIT versus Moderate intensity continuous training: Cardiovascular diseases**

Cardiovascular diseases are the global leading cause of death accounting for 19 millions of death annually according to WHO. Physical activity has a strong inverse relationship with the incidence and mortality of coronary arterial disease (CAD) and heart Failure (HF), to date cardiac rehabilitation a standard clinical procedure which can be conceptualized as a branch of cardiology. If implemented by a multidisciplinary work team it would allow the individual to be given a satisfactory clinical, physical, psychological and labor status [36]. For instance, cardiopulmonary fitness play a critical role in managing cardiovascular risk, with a 1-MET (metabolic equivalent; 3.5 mL/kg/min) increase translating into a 10% to 25% improvement in survival [37]. However, the best strategy to achieve higher METs is a matter of debate.

**Safety**

For decades, cardiac rehabilitation programs were based on MICT programs. However, emerging evidence that HIIT may exert superior or similar cardiovascular adaptations than MICT, raised concerns about the safety aspects of applying HIIT in cardiac patients with cardiovascular disease including increasing the risk of sudden cardiac death and myocardial infarction in susceptible persons. One study included nearly five thousand patients with CAD undergoing MICT and HIIT program from three Norwegian CR services. Data reported one fatal cardiac arrest (by 129.456 exercise/hour) in patients following MICT protocol, and two non-fatal cardiac arrests (by 46.364 exercise/hour) in patients following HIIT program [38]. The authors indicated that the risk of cardiovascular events is low, regardless of the exercise program for patients within CR programs.

More recently, a meta-analysis included 23 papers, 1117 participants (HIIT=547; MICT=570) to investigate the risk of exercise programs in patients with CAD and HF [39]. Again, data showed a low risk of major or minor cardiovascular events, and no difference for patients engaged in either protocol. Besides the relatively low risk of adverse cardiac events following HITT, prescribing one protocol or other should be based on patient’s conditioning, age, exercise background, and adaptability.

**Efficacy**

Improvements in cardiopulmonary fitness (VO₂max and VO₂peak) is a traditional endpoint for patients within cardiac rehabilitation, and stronger predictor of morbidity and mortality in patients with cardiovascular disease. In the last decades, a growing body of literature suggests that HIIT programs may exert greater VO₂ improvements than MICT in young healthy participants, depending on FIIT parameters [17]. Therefore, novel studies attempt to adjust HIIT programs for patients undergoing exercise intervention programs.

Two studies evaluated the efficacy of different HIIT protocols (intensity and rest interval) for patients with CAD [40] and HF [41]. Regardless the nature of heart pathology, patients with higher deconditioning reported more convenience, tolerance, and efficacy for HIIT protocols with short duration (15-30s) followed by the same time of passive recovery (15-30s), or 1:1 model. These models facilitate cardiac patients working at a higher intensity for a longer time. One consequence is to effectively improve VO₂peak. For patients who presented better fitness at baseline, they seem to tolerate longer bouts (~90s) followed by 90sec of active recovery. Combined, as long as patients improve their physical fitness, longer bouts of exercise and shorter period of rest interval will be well tolerated. Therefore, the flexibility of HIIT protocols permits adjustments to the full level of physical fitness. For example, WISLOFF, et al. [42], demonstrated superior results of a long HIIT model, 4 × 4 min - 90% to 95% peak heart rate for 3 mins of active recovery - 50% to 70% peak heart rate, compared to MICT, mainly in remodeling of the left ventricle, aerobic capacity, endothelial function and quality of life. Since the HIIT model used can bring different results depending on the shape
used in a given population. In a systematic review with metaanalysis, the authors investigated HIIT and their FIIT parameters on VO2 achievements in patients with CAD and HF. HIIT improved VO2 peak in both conditions. For patients with HF, intensities higher than 40% of VO2 peak during rest intervals and frequency above 2d/w were more favourable. For patients with CAD, durations below 12 weeks showed better results [43].

Is HIIT superior to MICT for inducing cardiovascular adaptations in patients with cardiovascular diseases? To address this question, one multicenter trial compared 12 weeks of HIIT or MICT in patients with HF and with reduced ejection fraction. There was no superiority of HIIT over MICT in VO2 peak improvements or in adverse events. In addition, none of these changes was maintained at follow-up after 52 weeks [44]. Two others systematic review with meta-analysis included 13 studies with HF patients [45], and other included 20 studies with CAD patients [46], the authors reported no significant differences to improve VO2 peak for participants inserted in either group.

Although HIIT seems to be a good clinical strategy, some points should be considered in applying this model. Patient adherence to the HIIT model was similar to the MICT during outpatient rehabilitation, but this is not seen when exercise was not supervised, clinical status, functional capacity and patient risk stratification are important factors to be considered when prescribing HIIT as an alternative to the MICT, and only introduce the HIIT after the patients present asymptomatic and stable responses to vigorous physical training (Table 1) [47–49].

Table 1: HIIT contraindications for patients with cardiac diseases [47,48].

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<td>Acute pulmonar embolus or pulmonar infarction</td>
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<td>Uncontrolled symptomatic cardiac arrhythmia causing hemodinamic compromise</td>
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<td>Thromplebitis</td>
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<td>Uncontroled Hypertnension &gt;180 /100 mmHg</td>
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<td>Severe dyspnea at rest and/or severe excercise intolerance</td>
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<td>Decompensated heart failure</td>
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<tr>
<td>Recent embolism</td>
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<td>Acute non-cardiac disorder that may be aggravated by exercise (i.e infection, renal failure, thyrotoxicosis)</td>
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HIIT versus Moderate intensity continuous training: Cancer

Cancer incidence and mortality are rapidly growing worldwide. According to the most recent World Health Organization [50] survey, cancer is expected to be the leading cause of death and the greatest barrier to increasing life expectancy in the 21st century. The causes of cancer statistics are complex, but the leading position of cancer also reflects the relative reduction in mortality rates of stroke and coronary heart disease. Another recurring observation is the rapid “westernization” of countries, which is strongly associated with pathogenesis of gastrointestinal tumors (esophagus adenocarcinoma, liver, stomach, colon, and rectum) and hormone-associated tumors (i.e breast, prostate, endometrium). A clear feature of “westernization” is poor dietary habits and lack of exercise. Since the late 80ths, exercise has been considered a plausible and effective strategy for patients with neoplasias [51].

In the last two decades, extensive review studies with meta-analysis confirmed exercise prescriptions as a safe and effective strategy to improve health and functional outcomes in patients with cancer [52,53]. For most solid cancers, radical surgery is the first-line treatment, and the single most important curative treatment modality, in better-conditioned individuals are at lower risk for postoperative complications [54]. As seen in a recent review where 167 patients with non-small cell lung cancer submitted to preoperative exercise intervention were associated with 67% reduction in risk of pulmonary complications [55]. EDVARSEN, et al. [56], using a concurrent model (endurance training, HIIT + resistance training) in patients with non-small-cell lung cancer (NSCLC), demonstrated increases in
cardiorespiratory function, maximal strength, and functional capacity. The authors of the study emphasized the importance of these patients being able to perform a high-intensity training soon after an important lung cancer surgery. This body of evidence stimulates several specialized agencies to publish exercise guidelines for patients with cancer [52,57].

In cancer, moderate to vigorous exercise intensity showed the best level of evidence to improve physical function and mitigate cancer-related impairments, than low-intensity exercise interventions [53]. However, an emerging body of literature suggests that HIIT protocols can induce different and/or additional benefits for people with cancer [15]. For patients with cancer, the calibrate HIIT protocols may be a strategy against the multicomponent cancer treatment (chemoradiotherapy, surgery, hormone therapy and immunotherapy) and time-related barriers such as busy medical appointments.

The field of exercise oncology is emerging, while some misconceptions still present. One key debate is to know if high-intensity exercise may lead to temporary immunosuppression and boost inflammatory response, which is a real concern for patients with cancer. While studies are limited with cancer population, there is growing evidence in younger that high-intensity exercise protocols (including HIIT) do not exacerbate immunosuppression or pro-inflammatory regulation, rather new findings indicated that exercise-induced immune cells redistribution to peripheral tissues [58]. Indeed, a redistribution of immune cells by exercise has been investigated in cancer models. Novel findings in rodents and cancer patients indicated that exercise promotes a natural killer (NK) cells distribution and help T-cells activation in tumor sites, a potential “immunotherapy” mediator [59,60]. In agreement, six weeks of HIIT protocol (10 sets x 60 sec at 90% HR max with 60sec interval) in obese women with breast cancer, or four weeks of HIIT in the obese mouse model, induced markedly increased in NK cells circulating number and activity in both models [61]. Importantly and aligned with the “intensity” principle, NK activation and redistribution are dependent on catecholamines (Adrenaline and Noradrenaline) [62]. Clearly, more research is needed in this area to understand how exercise and its principles exert their effects on cancer patients.

Safety

Evidence level that HIIT can be safe for patients with cancer is ongoing. One review study included ten studies conducted with 522 cancer patients, mostly with mixed cancer types, to report one serious adverse event with HIIT (seizure) in one patient with brain tumor, and two other studies with non-severe adverse events (hypotension) [15]. Thus, pooled information to date suggests that HIIT is safe, as MICT, for patients with cancer. However, some restrictions should be considered for patients with brain tumors or brain metastases. More research is warranted given potential benefits and safety concerns of HIIT for patients with cancer.

Efficacy

In the current exercise oncology literature physical training has been proposed to address and improve almost every imaginable outcome in cancer patients. Such results are broadly seen in psychosocial outcomes among which we enumerate: quality of life (QoL), depression, cancer-related-fatigue, anxiety, sleep quality, across direct physiological effects of the exercise training, such as fitness levels, oxygen consumption, muscle mass and strength [54]. The potential efficacy of HIIT programs for cancer survivors may encourage clinicians to consider exercise as a permanent strategy, especially for patients with time is a concern. The early evidence for feasibility, safety, and tolerability of high-intensity exercise for cancer patients appeared almost two decades ago. In 2003, Adamsen L, et al., [63] exposed 23 participants with heterogeneous cancer population undergoing chemotherapy to a mixed exercise training including, aerobic 60-100% of maximal heart rate, resistance 85-95% of one repetition max, followed by relaxation therapy. 85.2% of patients completed the program. Cardiorespiratory fitness and muscle strength increased after the intervention. Physical
wellbeing and depression tended to improve, but with lesser effect. The lack of a control group limits further interpretations.

In the last years two systematic reviews with meta-analysis [64,65], pooled the newest information of HIIT for patients with cancer. Combined, they included 21 studies, with 5 duplicates. Data showed that HIIT was performed from 3 to 6 weeks. The compliance was high and ranged from 74-97% among studies. Most of them investigated the effects of exercise protocols on cardiorespiratory fitness. There was robust evidence that HIIT protocol was superior to usual care improving VO\textsubscript{2} peak; whereas studies showed no difference compared with MICT. Therefore, the HIIT protocol induced similar cardiorespiratory gains within a shorter period of exercise exposure. This is relevant in the oncology setting since VO\textsubscript{2} was inversely associated with morbidity and mortality [66]. Additional outcomes included muscle strength, quality of life, body composition and fat mass. Despite the limited studies, there was a trend for a superior effect of HIIT compared with usual care, and again, no superiority of MICT. One relevant finding was the larger effect of HIIT to reduce fat mass compared with MICT [67]. Body composition has a key role to predict outcomes and treatment side-effects in patients with cancer [68]. Higher muscle radiodensity, meaning low fat infiltration in skeletal muscle, demonstrated an independent predictor factor of short term mortality in patients with gynaecological cancer [69]. The role of HIIT on skeletal muscle composition still uncertain and rises like a hot topic in oncology.

Several limitations remain before the broader utility of HIIT as an alternative in the cancer clinic. Firstly, the lack of standardization. Different from MICT the FITT principles differed widely among HIIT protocols. Precisely, there is no consent of VO\textsubscript{2}, maximal heart of BORG scale as a standard physiological parameter to prescribe intensity. Further, time interval and modality (active or passive) is critical for HIIT protocol and should be better elucidated for cancer survivors. Still, most studies included mixed cancer patients. In the era of multimodal treatment and molecular heterogeneity in the oncology field, further studies are warranted focusing on specific tumor populations.

**HIIT versus Moderate intensity continuous training: Type II Diabetes Mellitus (T2D)**

Higher rates of obesity and overweight are a global health problem. In 2016, there were 1.9 billions of adults in the category of above normal body mass index. From these, 13% (650 million) were obese. The great body of evidence links type 2 diabetes with obesity and a causal relationship between insulin resistance. Despite a clear relationship, there is a great difference between subcutaneous and visceral adipose tissue on T2D. An increase in subcutaneous adipose tissue has a mild impact on insulin resistance, whereas each standard deviation elevation in visceral adipose tissue mass increase insulin resistance in 80% [70]. Visceral adipose tissue underlies insulin resistance by many causes. Lipid accumulation and expansion occur in parallel in liver and muscle (80% of glucose clearance), contributing to insulin resistance. Further, adipose tissue indeed accumulates macrophages that release inflammatory cytokines, which can also impair insulin sensitivity [71]. Thus, treating adipose tissue, and mostly visceral adipose tissue, is a key strategy to reduce directly, or indirectly insulin resistance, and as consequence, T2D.

**Safety**

Exercise is the most effective way to improve cardiorespiratory fitness, and in the context of insulin resistance, exercise may induce additional benefits for glucose control [72]. For patients with diabetes, current guidelines recommend 150 min of moderate to vigorous exercise (40-60% of maximal aerobic capacity or 55-70% of HR\textsubscript{max}) and included two to three resistance exercise sessions per week [73]. For patients with T2D whom exercise habits are too low, a more vigorous exercise and low volume may be most effective to reduce hyperglycaemia. In fact, a meta-analysis study indicated the “intensity” parameter, rather than volume, as a stronger predictor exercise parameter for lowering blood glucose in patients with T2D [74]. Compared with cardiovascular diseases where authors reported an event rate
of 1 nonfatal heart attack per 23,182 hrs of HIIT [38], there is limited information assessing safety in patients with T2D undergoing HIIT.

**Efficacy**

In the last guideline of physical activity and exercise recommendations for people with diabetes, HIIT appeared as an alternative to be used. It's benefits includes rapid improvements in skeletal muscle oxidative capacity, insulin sensitivity and glycemic control [75]. One recent review including 41 studies indicated a superior effect of HIIT (~28%) reducing total fat mass compared with MICT, and no superior effect for body fat percentage [76]. However, the superiority of HIIT to reduced adipose tissue or body fat percentage remains contradictory [77,78]. Little is known regarding fat mass control in patients with T2D. A randomized control trial combined T2D (mean age 63 years) patients in one of these followed protocols using cycle ergometer. 1) HIIT (4min, at 90% of HRmax, 3 min active rest at 70% HRmax); 2) MICT (32 min at 70% HR max) or non-exercise for 8 weeks under supervision. There was no report of adverse effect or hospitalization. VO$_2$peak and exercise tolerance improved at the same magnitude in exercise groups, regardless of no change in body weight, adipose tissue and fat-free mass [79].

Blood glucose control is a hallmark in studies focusing on T2D. HIIT and MICT reduced insulin resistance in patients with T2D. One potential advantage of HIIT may be the persistent effect in glycemic control compared with MICT [80]. Other review included 50 studies, six focused on T2D, with HIIT for at least 2 weeks. The authors highlighted the largest effect of HIIT in patients with T2D and metabolic syndrome. The reduction in fasting glucose and HbA1c were pronounced when compared to the control group. Findings on fasting insulin were heterogeneous. It is interesting to note that improvements in cardiorespiratory fitness and body weight do not influence insulin resistance or glucose control.

Regarding potential mechanism to unveil how HIIT induced favourable changes in glycemic control and insulin resistance, the HIIT model reduced abdominal adiposity, which contributes to insulin sensitivity in the liver. Further, exercise at higher intensity depleted muscle glycogen more effective than continuous training. As a consequence, GLUT-4 is translocated to sarcolemma enable more efficient glucose uptake [81]. Finally, HIIT induced mitochondrial biogenesis and citrate synthase (CS) activity. In a small cohort with 8 patients with T2D performed 6 sessions of HIIT (10set/60sec at 90% HRmax, and 60 sec rest) for 2 weeks. The glycemic control was associated with higher muscle oxidative capacity and CS content [29].

**Conclusion**

As the safety of HIIT protocols is becoming more evident, the focus has shifted away for inclusion HIIT as therapy in the clinical setting. Despite a lower training volume, HIIT resulted in similar or even better improvements in the cardiorespiratory fitness, body fat and glycemic control compared to MICT (Table 2). HIIT, therefore, appears to be an important time-efficient treatment for individuals with cardiovascular diseases, cancer, and type II diabetes. The body of evidence concerning safety is growing. With a few exceptions (tumor brain or brain metastases), these data showed that HIIT sessions may be as safe as MICT for patients with cancer. Clearly, further data is warranted concerning the optimal HIIT session (e.g., interval number, mode, length, and intensity). For patients with higher deconditioning level, a shorter “on” bouts of exercise (lower than 4 min in total) and longer rest of interval may be advised to achieve a higher level of intensity (i.e 1:1 protocol). As patients are functionally progressing, exercise specialist may be capable to adjust for longer bouts and shorter interval resting time.
Table 2. Comparison of improvements in physiological parameters between HIIT and MICT (The arrows indicate the increase in improvements in the physiological parameters for each training type (HIIT x TCIM); ↑↑↑: Very good; ↑↑: good; ↑: little, or there was no significant difference; Arrow ↔ indicates little evidence; HIIT: High intensity interval training; MICT: Moderate intensity continuous training).

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<tr>
<th>Benefits of Exercise</th>
<th>Cardiovascular Disease</th>
<th>Cancer</th>
<th>Type 2 Diabetes</th>
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In a global scenario where “lack of time” is the leading barrier for not regularly active life, these data advocate the incorporation of HIIT protocols as a valid tool for patients with chronic diseases. Increase exercise “portfolio”, safely and adapted to each patient functional condition and preferences, maybe the greatest allied against extensive inactivity excuses for patients living or at risk for chronic diseases.

Conflict of Interest
The authors declare there are no conflict of interest.

References