

Effects of Physical Activity and Type 2 Diabetes

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Type 2 diabetes mellitus (T2DM) is one of the most widespread diseases worldwide. Lifestyle interventions, including diet and physical activity (PA), are fundamental non-pharmacological components of T2DM therapy. Exercise interventions are strongly recommended for people with or at risk of developing or already with overt diabetes, but adherence to PA guidelines in this population is still challenging. Furthermore, the heterogeneity of T2DM patients, driven by differing residual β -cell functionality, as well as the possibility of practicing different types and intensities of PA, has led to the need to develop tailored exercise and training plans.

type 2 diabetes

physical activity

exercise

β -cell function

insulin resistance

1. Introduction

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by high glucose levels, driven by the disruption of the physiologic balance between tissue sensitivity to insulin action, changes in plasma glucose and insulin secretion, β -cell function, and mass. In particular, impairments in β -cell function [1][2] can affect the dynamics of insulin secretion even at a very early stage of the disease [3][4]. The increased morbidity and mortality in T2DM patients [5] can be mostly ascribed to metabolic dysregulation and chronic inflammation leading to atherosclerotic cardiovascular disease (ASCVD). Lifestyle interventions, including appropriate diet and physical activity (PA), constitute an important non-pharmacological aspect of T2DM therapy, and their effectiveness in the prevention of T2DM-associated ASCVD has been amply demonstrated [6]. PA improves glycemic control [7] in patients with diabetes by enhancing insulin secretion and insulin sensitivity [8][9], and by stimulating glucose uptake by skeletal muscle and reducing body weight against a background of poor β -cell function. In addition, PA may counter inflammation related to pancreatic β -cell dysfunction [10] via circulating mediators, reducing oxidative stress and increasing the levels of antioxidants [11][12][13]. In this regard, some meta-analyses have shown that aerobic training, resistance training, and the combination of the two improve glycemic control and HbA1c levels [14][15][16], together with significant improvements in anthropometric, cardiovascular, and metabolic risk factors [16][17]. Other studies have found associations between PA and diabetes remission rate in newly diagnosed subjects [18][19][20]. Anyway, it should be underlined that improvements in glucose tolerance and glucose homeostasis were only achieved through PA in combination with pharmacologic treatment and/or an appropriate dietary regimen in these

studies, providing evidence that PA is a necessary, but not sufficient, strategy for achieving partial or complete remission from the disease.

2. Effects of Physical Activity on β -Cell Function and Insulin Secretion

Insulin resistance and β -cell dysfunction are fundamental metabolic defects of T2DM, and these conditions are already partially present in obese subjects with prediabetes [21]. The preservation of residual β -cell function in individuals with obesity and IGT—who have already lost up to 50–70% of β -cell function—is an effective strategy to prevent T2DM [22][23]. The mechanism linking PA and β -cell function is still not fully understood; however, it has been demonstrated that exercise interventions and correct dietary management may protect β -cell function by reducing metabolic stress [24]. Exercise training has a potential role in preserving β -cell health, and, therefore, represents an effective strategy to prevent or delay diabetes onset in individuals at risk of or already affected by the disease; moreover, PA supports pharmacological effectiveness to prevent β -cell failure [10].

It can be difficult to estimate the relative contribution of a single type of PA to β -cell protection, as well as the correct timing for exercise interventions in patients with metabolic impairments, but there is evidence that exercise, when started at an early stage, may delay disease progression by increasing β -cell resistance to endoplasmic reticulum (ER) stress [25] and other mediators of immune damage [10]. Several trials have studied the effect of exercise on insulin secretion in individuals with T2DM and prediabetes [8][9][26][27][28][29][30][31][32][33], as well as in sedentary overweight or obese subjects [8][31][32][34][35][36][37]. Some of these studies have investigated the effects of different intensities of aerobic training [8][9][26][28][30][31][32][33][36], while others have evaluated high-intensity interval training (HIIT) [38][39], resistance training [27][32], and simultaneous aerobic and resistance training or a combination of the two [34][35][37] on metabolic outcomes.

In conclusion, in the cited trials, it is important to note that only interventions lasting more than 2 months resulted in improvements in insulin secretion, and that all training regimens led to benefits regarding insulin secretion. This emphasizes that significant results can only be achieved following an appropriate exercise program, whereas random exercise sessions might not result in significant improvements in glucose metabolism or cardiovascular outcomes.

3. Responsiveness to Physical Activity

Despite the well-recognized positive impact of PA on β -cell function and insulin secretion, individuals with different secretory functions at baseline may show different responses to interventions, and a variable proportion of patients have been described as exercise resistant in several studies. Dela et al. [9] stratified patients with T2DM into “moderate” and “low” secretors according to individual C-peptide responses to an intravenous glucagon test. They found that only moderate secretors obtained positive responses from an aerobic training program, thus highlighting that a residual β -cell secretory capacity is required in order to maximize the beneficial effect of aerobic exercise on glycemic control. In addition, to further investigate how baseline β -cell function may influence training-induced

changes in glycemic control, the HERITAGE study [30] assessed insulin secretion patterns during an IVGTT in a large heterogenic population to detect possible differences in β -cell functional effects in response to a 20-week endurance training program (cycle ergometers 3 days/week for 60 sessions). Participants with better glucose tolerance at baseline showed reduced insulin secretion following regular exercise, while those with poorer glucose tolerance at baseline showed an increase in insulin secretion after exercise. These results suggest that intersubject variability in baseline β -cell function could partially explain the different effects of exercise on glucose homeostasis. In this context, intersubject variability in basal insulin secretion could provide an effective explanation for the different secretory responses to exercise and should be considered when prescribing tailored and individualized treatments. Consistently, another study confirmed this variability by demonstrating that long-term exposure to hyperglycemia –leading to reduced β -cell function [40] and low insulin secretory function—before the introduction of PA predict a poorer training-induced outcome. Thus, aerobic exercise may be less effective in improving glucose control in patients with poorly controlled long-term T2DM. Accordingly, another study [32] confirmed that the response to exercise in prediabetic and diabetic subjects largely depends on basal β -cell function: in particular, basal HbA1c, BMI, and β -cell function were all predictors of exercise response in elderly patients with prediabetes; by contrast, the type of PA did not predict the effectiveness of the response. In this context, residual β -cell function should be restored through appropriate pharmacological treatment by eliminating the noxious effects of gluco- and lipotoxicity before therapeutic aerobic exercise can provide effective improvements in glucose homeostasis. Collectively, these data strongly support the need for individualized treatments in order to maximize the benefit of exercise.

A recent study [18] investigated the effectiveness of a 12- or 24-month intensive lifestyle program in inducing partial or complete T2DM remission compared to standard of care, demonstrating that 23% of participants in the lifestyle intervention group met the criteria for any T2DM remission compared to 7% in the standard care group. Further, the highest remission rate was obtained in participants with well-controlled short-duration T2DM.

4. Exercise Regimens for T2DM

As shown in **Table 1**, many types of PA can improve glycemic control and lead to overall benefits in people with T2DM. To date, aerobic and resistance training, and the combination of both, have formed the cornerstone of lifestyle intervention for T2DM patients, as previously mentioned. Aerobic training, like running and cycling for about 1 h, is a moderate-intensity type of PA and represents the best activity to reduce body fat mass when required. Moreover, it leads to improvements in oxygen transport and metabolism in the skeletal and heart muscle [41]. Resistance training, on the other hand, is strength-building, as it increases lean body mass, and is characterized by short-term exercise repetitions performed by using, for example, external resistance tools like dumbbells, kettlebells, and barbells, or using body weight, weight machines, or elastic resistance bands.

Table 1. Type of physical exercise for adults with T2DM.

Type of	Description	Intensity	Frequency	Duration	Proven	Additional
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Exercise					Benefits	Specification
Aerobic Training	Rhythmic and repetitive PA that uses large muscle groups, e.g., running, cycling, swimming, dancing, jogging	Moderate (55–74% HRmax) or Vigorous (75–95% HRmax)	5–7 d/week with no more than two consecutive days between bouts	At least 30'/session for $\geq 150'$ /week of moderate activity or $\geq 75'$ /week of vigorous activity (or an equivalent combination of moderate- and vigorous-intensity, preferably spread throughout the week).	<ul style="list-style-type: none"> ↓ Glycemia with fewer daily hyperglycemic excursions ↓ HbA1c ↑ Insulin sensitivity ↓ Blood lipids ↓ BP ↑ Fitness levels, even without weight loss 	-
Resistance Training	Short-term repetition exercises performed using external resistance tools like dumbbells, kettlebells, and barbells, or using body weight, weight machines, or elastic resistance bands	Moderate (50–69% of 1-RM) or Vigorous (70–85% of 1-RM)	2–3 d/week on non-consecutive days	10–15 repetitions/set with 1–3 sets per type of specific exercise	<ul style="list-style-type: none"> ↑ Strength ↑ Bone mineral density ↑ Lean mass ↓ BP ↓ Blood lipids ↑ Insulin sensitivity ↓ HbA1c 	-
Pilates	Specific targeted exercises to improve strength, flexibility, and posture, with particular focus on the core	Light	≥ 2 –3 d/week	-	<ul style="list-style-type: none"> ↑ Blood glucose management ↑ Functional capacity 	For patients with low levels of fitness and insufficient balance
Yoga	Breath, movement,	Light	≥ 2 –3 d/week	-	<ul style="list-style-type: none"> ↓ HbA1c ↓ Blood lipids 	For patients with low levels

	and meditation to unite mind, body, and spirit				↑ Improvement of body composition	of fitness and insufficient balance	
Balance	Focuses on the ability to maintain proper posture and refers to exercises that are designed to improve and maintain balance	Light	≥2–3 d/week	-	-	↓Risk of falls by improving balance and gait, even in adults with peripheral neuropathy	
Flexibility	Stretching and moving a joint through its range of motion	Light	≥2–3 d/week	10"–30" per stretch (static or dynamic) group; 2–4 repetitions of each	-	↑ Joint range-of-motion; facilitates participation in activities that require flexibility	
HIIT F-HIT	HIIT: repetitions of short intervals of vigorous aerobic training (running or cycling) alternating with a short period of active or passive recovery. F-HIT: based on real-world situational exercises at a high intensity by combining resistance training, gymnastics (body	Vigorous (75–95% HRmax) follow by active or passive recovery	3 d/week	Repetitions of 10"–4' of vigorous activity with 12"–5' of active or passive recovery	↑ Insulin sensitivity ↑ β-cell function in T2DM with preserved residual β-cell secretory capacity ↑ Fitness levels ↓ HbA1c ↓ BMI ↑ CGM	-	...; ain , 783– of em. , E.C.; n Direct ;

Capece, U.; Quero, G.; Pontecorvi, A.; et al. Pancreaticoduodenectomy Model Demonstrates a Fundamental Role of Dysfunctional β Cells in Predicting Diabetes. *J. Clin. Investig.* 2021, 131, e146788.

weight), and aerobic exercise

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Himmelfarb, C.D.; Khera, A.; Lloyd-Jones, D.; McEvoy, J.W.; et al. 2019 ACC/AHA Guideline on Key and abbreviations: ↑: increased; ↓: decreased; HIIT: high intensity interval training; F-HIT: functional high-intensity training; T2DM: type 2 diabetes mellitus; HbA1c: glycosylated hemoglobin; 1-RM: 1-repetition maximum; Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation* 2019, 140, e596–e646. HRmax: heart rate max; BMI: body mass index; CGM: continuous glucose monitoring; BP: blood pressure; PA: physical activity.

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“Lack of time” represents one of the main reasons for non-adherence to therapeutic exercise programs. Thus, additional efforts are needed in order to promote greater adherence to guidelines by prescribing tailored PA programs. In addition, it should be considered that the extent of the beneficial effects—such as the improvement of

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