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The importance of exercise for glycemic control in type 2 diabetes ☆

U.S. Afsheen Syeda [a,1], Daniel Battillo [b,1], Aayush Visaria [c], Steven K. Malin [b,c,d,e,*]

[a] Department of Nutritional Sciences, Rutgers University, New Brunswick, NJ, United States
[b] Department of Kinesiology and Health, Rutgers University, New Brunswick, NJ, United States
[c] Center for Pharmacoepidemiology and Treatment Sciences, Rutgers Institute for Health, Health Care Policy, and Aging Research, New Brunswick, NJ, United States
[d] New Jersey Institute for Food, Nutrition and Health, Rutgers University, New Brunswick, NJ, United States
[e] Institute of Translational Medicine and Science, Rutgers University, New Brunswick, NJ, United States

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ABSTRACT

Exercise is a first-line therapy recommended for patients with type 2 diabetes (T2D). Although moderate to vigorous exercise (e.g. 150 min/wk) is often advised alongside diet and/or behavior modification, exercise is an independent treatment that can prevent, delay or reverse T2D. Habitual exercise, consisting of aerobic, resistance or their combination, fosters improved short- and long-term glycemic control. Recent work also shows high-intensity interval training is successful at lowering blood glucose, as is breaking up sedentary behavior with short-bouts of light to vigorous movement (e.g. up to 3min). Interestingly, performing afternoon compared with morning as well as post-meal versus pre-meal exercise may yield slightly better glycemic benefit. Despite these efficacious benefits of exercise for T2D care, optimal exercise recommendations remain unclear when considering, dietary, medication, and/or other behaviors.

Introduction

Approximately 10.4% adults in the U.S. have type 2 diabetes (T2D), 3.8% of whom are undiagnosed. In addition, nearly 45.8% of adults are also categorized as having prediabetes, thereby placing major financial strains on the healthcare system.[1] T2D (and prediabetes) is mainly characterized by reduced whole-body insulin sensitivity and β-cell dysfunction. Low insulin sensitivity initially induced by overnutrition and/or physcil activity, for instance, promotes hypersecretion of insulin from pancreatic β-cells to regulate circulating glucose. When insulin secretion is no longer able to compensate for the prevailing low insulin sensitivity, blood glucose levels worsen towards prediabetes and T2D status. While the exact cause of T2D remains an area of intense research, excess body weight serves as a leading risk factor. Indeed, excess lipid accumulation surrounding vital organs in the abdomen (i.e. visceral fat), as well as within liver and muscle cells, are thought to impair insulin signaling and induce insulin resistance.[2] Given that more than 42% of American adults have obesity,[3] it is no surprise that identification of optimal treatment plans to combat obesity related insulin resistance is warranted to manage blood glucose.[4] One such treatment option is physical activity and/or exercise. Physical activity is broadly defined as any bodily movement that is above resting conditions, whereas exercise is planned or structured movement with specific intent on gains in aerobic and/or muscular fitness. Most recommendations by the American College of Sports Medicine (ACSM) and/or American Diabetes Association (ADA) for physical activity/exercise focus on frequency, intensity, and modality to favorably impact glycemic control.[5,6] Included within modality are considerations including volume or the duration/repetitions of the exercise being completed. Additionally, aerobic exercise intensity is primarily determined using a percentage of one's maximal heart rate (%HRmax) and maximal oxygen consumption and utilization (%VO_2max).[5,6] It is also worth mentioning that rating of perceived exertion (RPE) is a practical tool people can use to estimate exercise intensity if they are unable to use heart rate or have maximal fitness tests conducted.[5,6] Typically RPE correlates well with heart rate (e.g. RPE of 12 would theoretically relate to a HR of 120 bpm). Herein, we compare aerobic, resistance, and concurrent exercise, defined as completing aerobic and resistance exercise in combination, as modalities to affect insulin sensitivity and cardiometabolic health. We also discuss whether intensity or timing of exercise throughout the day matters to yield optimal effects on glucose control. In turn, we discuss high intensity interval versus continuous exercise for glycemia followed by the timing at which exercise is performed. Recognizing that some people may find it challenging to dedicate time to exercise, we also review breaks in sedentary behavior as a strategy to manage blood glucose. Further, since weight loss can be quite variable in response to

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* Corresponding author at: Department of Kinesiology & Health, 70 Lipman Dr, Loree Gymnasium, New Brunswick, NJ 08091, United States.
E-mail address: steven.malin@rutgers.edu (S.K. Malin).
[1] Shared first author responsibility.

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exercise, we discuss current thoughts on weight loss variability, in addition to exercise benefits independent of weight loss, to help highlight benefits for people with T2D. Lastly, given many suggest individuals progress from obesity with normoglyceemia to prediabetes to T2D, it is understood that the pathology of insulin resistance is a continuum.[7] As such, the utlity of exercise in prediabetes and T2D will be discussed throughout. Together, future direction for the field and practical considerations is provided.

Type 2 diabetes prevention and management

It comes as no surprise that ACSM and ADA recommend comprehensive lifestyle programs that increase physical activity in effort to prevent glucose levels from detoriating as well as manage glycemia within a given range.[8,9] Indeed, lifestyle recommendations for individuals at risk for T2D often target weight loss of ~ 5-10% and an increase in physical activity to either 150 min/week or more of moderate intensity or 75 min/week of vigorous intensity aerobic exercise. Lifestyle interventions consisting of increased physical activity (i.e. aerobic and/or resistance exercise) and low-fat diet promotes ~5 kg weight loss for 2 years or beyond and lowers T2D risk by ~ 45%.[10] Interestingly, there appears to be a dose-response relationship with weight loss and glycemic control as reflected by HbA1c, a measure of average blood glucose levels over an 8-12-week period. Indeed, a 2-10% reduction in body weight between 1-4 years is paralleled by decreases in HbA1c of 0.2-1.0%.[6,10] This improvement in glycemic control is clinically meaningful as lifestyle prescriptions of >5% weight loss via reductions in total fat under 30% of total calorie intake (with < 10% coming from saturated fat), elevation in fiber consumption (i.e. 15g per 1000 kcal) and increases in physical activity (30 min/d) lowered the cumulative incidence of diabetes by 58% in people with prediabetes, compared with controls.[11] In the landmark U.S. Diabetes Prevention Program (DPP),[12] new cases of T2D were reduced by 58% in people with prediabetes. This reduction was achieved using an intervention based on 150 min/wk of physical activity and weight loss of approximately 7%,[13] although subjects who lost the most weight and met physical activity/diet targets had > 90% risk reductions of diabetes. Subsequently, it seems reasonable to ask whether weight loss is best achieved by activity and/or diet, provided its importance in promoting glycemic control. No randomized controlled trials to date, though, have directly compared caloric restriction to exercise versus caloric restriction plus exercise in people with T2D. However, Weiss et al.[14] observed that caloric restriction and exercise training in combination improved glucose tolerance and increased insulin sensitivity, using a 2-hr frequently sampled oral glucose tolerance test (OGTT), more than caloric restriction or exercise alone, among overweight sedentary adults. Conversely, post-prandial GLP-1 decreased in the caloric restriction group only, suggesting mechanisms affecting glucose tolerance may be different based on how weight loss is achieved. Interestingly, we identified similar observations to this in prior work after only 2 weeks of exercise, and this was correlated with gains in pancreatic β-cell function and GLP-1 increases,[15] although improvements in circulating adipose-derived inflammation were similar in these women with obesity.[16] In either case, adding exercise to caloric restriction will yield gains in aerobic fitness, which benefits quality of life. Additionally, adding exercise to caloric restriction improved weight regulation, such as high intensity interval exercise (60 min/day alternating 3 min at 90 and 50% peak HR), suppressed acylated ghrelin and increased fullness during caloric restriction, compared with caloric restriction only,[17] thereby favoring appetite suppression and increased satiety. This observation is consistent with exercise decreasing visceral fat during caloric restriction. Indeed, in the REverse metabolic SyndrOme by Lifestyle and Various Exercises (RESOLVE) trial, middle-aged to older adults with obesity underwent different modalities of high-volume exercise (15-20 hr/wk) combined with a high protein, caloric-deficit diet to determine effects on visceral fat. Participants between ages 50-70 yr were divided into three groups with varying intensities: moderate-resistance-moderate-endurance, high-resistance-moderate-endurance, and moderate-resistance-high-endurance. Following a 3-wk supervised program and continuing a self-management compliance protocol for the remaining 11 months, participants in the high resistance exercise group lost the greatest amount of visceral fat throughout the year-long combination program. This is consistent with recent evidence from the DPP that physical activity, independent of weight loss, is an independent predictor in prevention of T2D in the original cohort.[20] Nearly 2 decades since the DPP was originally published, this lifestyle program is now widely implanted in the U.S., with 1-on-1 counseling sessions both in-person and virtually. Many insurance programs (including Medicaid and Medicare) cover such treatment. Still, it is worth noting that while weight loss is a significant predictor of T2D prevention, the DPP standards have been updated. In fact, the goals of the program look to emphasize more the importance of physical activity, as standard advice was originally focused on losing 5-7% body weight to elicit favorable HbA1c levels. Now, the goal of 4% weight loss with 150 min/wk of physical activity, along with reduction in HbA1c of 0.2%, has been incorporated.[19] Taken together, exercise favors glucoregulatory effects via both weight-loss and weight loss-independent mechanisms[18] and highlights exercise for glycemic management (Fig. 1).

Type 2 diabetes reversal

Classic work from nearly 4 decades ago highlight that 12 months of high intensity exercise (about 85% HRmax 5 d/wk.) is capable of reversing and normalizing blood glucose in people with prediabetes and T2D.[21] We too have shown that as little as 2 weeks of high intensity interval or moderate continuous exercise is able to reverse prediabetes in nearly 40% of participants.[22] Nevertheless, it should be acknowledged that not all people with hyperglycemia may respond favorably to exercise. In fact, some studies suggest upwards of 10-30% of people with T2D may not improve fasting glucose and/or HbA1c following lifestyle therapy.[23] This is consistent with recent work showing no glycemic benefit to lifestyle therapy in people with T2D versus control, although lifestyle did reduce glucose medication numbers to a significant extent (about 75% vs. 47% discontinuation) in relation to greater exercise volume engagement.[24] This later work is of importance because it is consistent with work comparing the DPP program with the optimal intensity of exercise for preventing progression to T2D.[25] In short, these later results showcased that performing moderate intensity exercise of high volume (50% VO_2peak for about 287 min/wk) was most effective at improving glucose tolerance with only 2 kg of fat loss, when compared with high intensity and volume (75% VO_2peak for about 195 min/wk) or low volume moderate intensity (50% VO_2peak for 181 min/wk). While intensity effects may be somewhat unclear (*see below*), current work highlights higher volumes appear related to greater glucose regulation[26-30] and cardiometabolic health.[31] Indeed, a meta-analysis confirmed that engaging in 5-7 hr/wk of leisure-time physical activity or moderate to vigorous exercise was inversely related with risk of developing T2D.[22,32] Furthermore, the Look AHEAD (Action for Health in Diabetes) trial,[33] the longest running interventional study with median of 9.6 years, tracked the development of cardiovascular disease among patients with T2D. Subjects were randomized to either Intensive Lifestyle Intervention (ILI) including calorie restriction and increased physical activity or a control group that received Diabetes Support and Education (DSE). Under the monitoring of a registered dietitian, psychologist, and exercise physiologist, the intervention group ate a low calorie diet (LCD) between 1200-1500kcal/day, with <30% kcal from fat, setting a goal of 175 min of unsupervised exercise per week. By year 1, the ILI participants achieved 20.4% increase in their fitness levels, compared to the 5% in the DSE group. Throughout the trial period, the ILI group accomplished 3 to 6 times more remission of T2D than the control group among participants that were relatively healthy at baseline with a lower HbA1c and had T2D for a shorter duration. Interestingly, though,

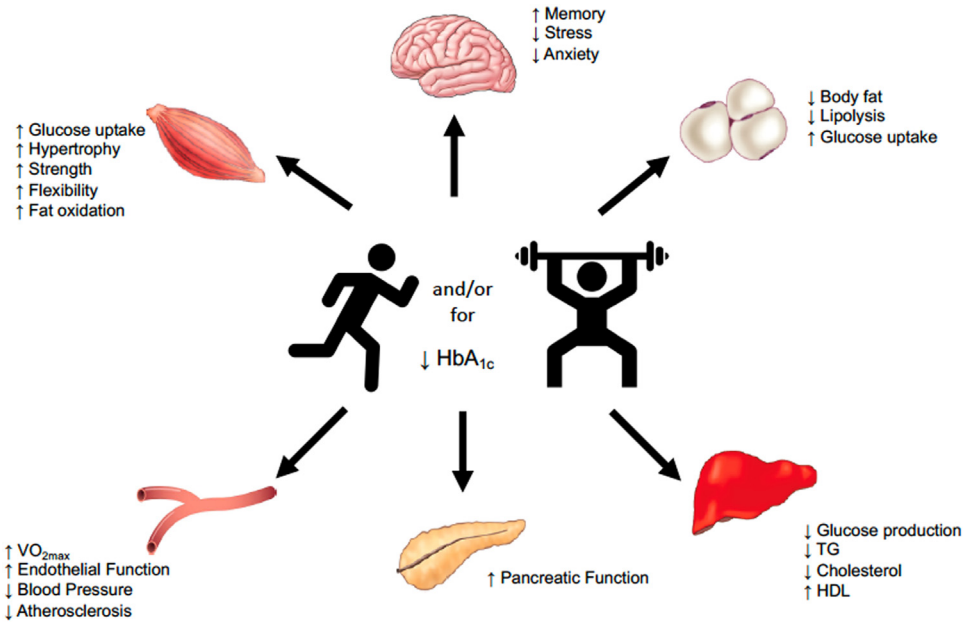

Fig. 1. Benefit of exercise on multiple bodily tissues for blood glucose control.

there was no significant improvement in rate of CVD events between the ILI and DSE groups. Nonetheless, the Diabetes Intervention Accentuating Diet and Enhancing Metabolism (DIADEM-I)[33] was a recent diet and physical activity-based, randomized controlled trial among adults (mean age 42.1 yrs) with T2D in the Middle East and North African regions. Participants were randomized into a control group on diabetes care or a lifestyle intervention group with total diet replacement (low-kcal/low glycemic index) and physical activity recommendations (target 10k steps/d for 150 min/wk), for a duration of 12 weeks. At the end of 1 year follow-up, there was sustained weight loss, with 61% no longer having T2D and 33% of participants going into remission. Weight-loss induced management of T2D in the lifestyle intervention group was also associated with improved CVD health and quality of life.[34] These findings together highlight that T2D is not inevitable and can be delayed, prevented, and reversed by exercise.

Aerobic compared with resistance exercise for glycemic control

Most work surrounding exercise on glycemic control has focused on aerobic exercise in people with prediabetes or T2D. Aerobic exercise is rhythmic in nature, with large muscle groups acting to support walking jogging, running, and cycling. Aerobic training increases insulin sensitivity and vascular function among other factors, such as aerobic fitness and reductions in body fat.[6] ACSM and ADA guidelines recommend at least 150 mins/wk of moderate-to-vigorous intensity aerobic activity spread out over at least 3 d/wk, with no more than 2 consecutive days without activity (Table 1). This frequency recommendation is mainly due to beneficial effects of aerobic exercise on insulin sensitivity lasting up to about 48 hr.[35,36] Indeed, skeletal muscle plays a paramount role in glycemic control, by virtue of exercise-induced blood glucose uptake and augmented insulin sensitivity, following an exercise bout. There are two primary pathways that promote skeletal muscle glucose uptake, insulin *in*dependent and insulin dependent.[37] During bouts of aerobic exercise, skeletal muscle promotes GLUT-4, a key transporter, to translocate to the cell membrane, to increase glucose uptake independent of insulin. Thereafter, these effects of exercise wane after about 3-6 hr, such that the muscle is now sensitized to insulin. This insulin sensitizing effect can last upwards of about 48 hr,[35,36] based on intensity, diet, and other factors (e.g. sleep, etc.). As such, single bouts of exercise are known to favorably impact insulin sensitivity and favor blood glucose control, prior to weight loss or gains in aerobic fitness.[38] Importantly, exercise further lowers subsequent risk of developing hypoglycemia among T2D patients who are non-insulin users.[81] Thus, accumulating bouts of exercise will not only favor insulin sensitivity, but also contribute to gains in aerobic fitness for reducing CVD and all-cause mortality in T2D, independent of body weight.[39]

Convincing evidence demonstrates that exercise can improve glycemic control. For instance, 6-months of aerobic training among overweight individuals with T2D, comprised of 4 sessions/wk at 45-60 min/session at 50-75% VO_2peak, reduced fasting plasma glucose (-18.58 mg/dl) and insulin levels (-2.91 mU/l) measured, when compared with a non-exercise control group.[40] Further, aerobic exercise consisting of 60 min at ~75% VO_2peak intensity for 4-5 d/wk over 12-16 wk reduced fasting blood glucose (-6.3 mg/dl) and increased insulin sensitivity in those with impaired glucose tolerance or T2D.[34] These findings are clinically relevant as epidemiological studies report a 21% reduction in diabetes-related death following a 1% decrease in HbA1c.[41] Moreover, a meta-analysis of 504 participants across 12 trials of aerobic and 2 trials of resistance training demonstrated a significant decrease in post-intervention HbA1c in the exercise groups by 0.66%, compared to the control group, independent of weight loss.[42] Interestingly, recent interest and advice on using continuous glucose monitoring (CGM) has grown in the diabetes community, in effort to provide a more accurate insight to acute changes in glycemia within individuals. A recent meta-analysis of 11 aerobic and resistance exercise interventions conveyed significantly decreased average glucose concentrations (-14.4 mg/dl) as assessed by CGM.[43] Importantly, this meta-analysis highlights that people spend on average approximately 129 minutes less in hyperglycemic ranges (i.e. >180 mg/dl), thereby reducing risk of complications. This aligns with findings that aerobic exercise also protects against CVD risk, beyond glycemic improvements. A meta-analysis with 1,003 people with T2D demonstrated that aerobic exercise training interventions lowered systolic blood pressure (-5.6 mmHg), diastolic blood pressure (-5.5 mmHg), triglyceride levels (-0.3 mmol/l), and total cholesterol (-0.3 mmol/l).[44]

Discerning the health benefits of resistance compared with aerobic exercise is useful for providing training diversity and augmenting exercise adherence. Given T2D is an independent risk factor for low muscular strength and accelerated decline in muscle mass/functional status, resistance exercise could be a viable strategy to combat risk in falls and dissuade sarcopenic (age-associated decline in muscle mass) losses.[45] Resistance or strength training specifically involves the contraction of

Table 1
Exercise training recommendations for adults with type 2 diabetes.

Type of Training	Type	Intensity	Frequency	Duration
Aerobic	- Rhythmic activities using large muscle groups, like walking, jogging, and cycling	- Moderate intensity exercise at 55-74% HRmax - RPE 12-13 (somewhat hard) - Vigorous intensity exercise at 75-95% HRmax - RPE 14-16 (hard to very hard)	- 3-7 d/wk, with no more than 2 consecutive days between exercise bouts. Daily exercise is suggested to maximize insulin action	- Minimum of 150 min/wk of moderate activity or 75-150 min/wk of vigorous activity, or an equivalent combination of the two
Resistance	- Contraction of muscle against an external force using free weights, weight machines, body weight, or elastic resistance bands	- For moderate intensity, repetitions of an exercise at a weight that can be repeated no more than 15 times. For vigorous intensity, repetitions of an exercise at a weight that can be repeated no more than 6-8 times	- 2-3 nonconsecutive d/wk	- 10-15 repetitions per set with 1-3 sets of each exercise. 8-10 exercises involving the major muscle groups in total
High Intensity Interval Training (HIIT)	- Alternating vigorous intensity exercise (aerobic or strength training) with recovery stages	- Vigorous intensity (75-95% HRmax) exercise, followed by active or passive recovery (30-60% HRmax)	- 3 d/wk for vigorous aerobic training, with not more than 2 consecutive days between bouts - 2-3 nonconsecutive d/wk for resistance training	- 10 seconds to 4 min of vigorous intensity exercise, with 12 seconds to 5 min of active or passive recovery
Breaks in sedentary behavior	- Walking or simple resistance activities (half-squats, calf raises, gluteal contractions and knee raises), or standing time in lieu of sitting time	- Light to moderate intensity exercise at 45-55% HRmax - RPE 10-11 (very light to fairly light)	- Every 30 min for 8 hr, given the increased risk of sedentary behavior beyond 8 hr/d	- Replace sitting time with standing time (2.5 hr/d) - Light-intensity walking (2.2 hr/d), in 3-min segments every 30 min

Note: Rating of perceived exertion (RPE) is a practical tool people can use to estimate exercise intensity. While not considered as accurate as using physiologic markers (e.g. heart rate), RPE typically correlates with heart rate (e.g. RPE of 12 would theoretically relate to a HR of 120 bpm). Thus, it is an acceptable tool to use.

muscle against an external force and includes using free weights, weight machines, body weight, or elastic resistance bands. ACSM and ADA recommend resistance training at least 2-3 nonconsecutive d/wk with moderate to vigorous training as determined by the number of repetitions an individual is doing per set (Table 1). If one can do a higher number of repetitions at a given weight – closer to 15 reps at a weight that can be repeated no more than 15 times – this is moderate exercise. Vigorous exercise follows the same principle around 6-8 reps. ACSM and ADA state that starting at moderate training involving 10-15 reps/set and increasing weight only when the target number of reps can be completed without reaching fatigue-induce failure is best practice. Vigorous exercise may be performed once technique and confidence in movement patterns occur.[6]

Resistance training conveys potent benefits to glycemic control and provides additional benefits to muscular strength, bone density, and quantity/quality of muscle. A meta-analysis of over 8500 patients with T2D found significant reductions in HbA1c of -0.57%, following structured resistance training, when compared with non-exercise control groups. This reduction in HbA1c, while clinically meaningful, is worth discussing since it reflects both fasting and post-prandial averages.[46] Recent work has suggested that resistance training does not significantly affect fasting glucose. As such, it appears that the benefit of resistance exercise may be driven in the post-prandial state. This would be consistent with studies reporting that resistance exercise training augments insulin sensitivity by 48% as measured by the euglycemic-hyperinsulinemic clamp (i.e. a "gold-standard" approach). Interestingly, skeletal muscle is responsible for ~80% of insulin mediated glucose uptake.[47] Thus, targeting increased muscle mass and/or quality with resistance exercise seems appropriate to reduce blood glucose in T2D. In parallel, a meta-analysis of 14 studies reported that resistance training in T2D lowered total cholesterol, LDL cholesterol, and triglycerides.[48] Recently too, a supervised progressive high-intensity resistance training program performed 3 d/wk for 6 months in older patients with T2D significantly decreased both systolic and diastolic blood pressure.[49]

Given that the mechanisms by which aerobic and strength training may reduce HbA1c differ, combining training programs may yield greater benefit. A combined aerobic resistance training regimen (30 min aerobic at 40-80% HRR, plus 30 min resistance training at 40-60% 1-RM for 6 exercises of 12 reps) decreased fasting blood glucose (-36 mg/dl), triglycerides (-106 mg/dl), and significantly increased fat free mass (+0.4 kg).[50] A meta-analysis of 915 participants across 14 trials compared the glycemic benefits across aerobic, resistance, and concurrent training, through reductions in HbA1c. While both modalities conveyed reductions in HbA1c, concurrent training saw the greatest reduction in HbA1c (-0.17%), fasting glucose (-35.82 mg/dl), and triglycerides (-0.28 mmol/l).[51] Together, this evidence supports the notion that concurrent training may be the most efficacious modality to improve glycemic control and blood lipids. The Health Benefits of Aerobic and Resistance Training in Individuals with Type 2 Diabetes (HART-D) and Diabetes Aerobic and Resistance Exercise (DARE) randomized controlled trials examined the effects of aerobic, resistance, and concurrent training regimens in people with T2D. While the DARE trial[52] (Aerobic: 15-20 min at 60% HRmax progressed to 45 min at 75% HRmax, resistance: eight weight bearing exercises with progressive load increase, 2-3 sets with eight rep max, aerobic + resistance) reported reductions in HbA1c across all three exercise groups, the concurrent group reduced HbA1c the most (-0.46% vs. aerobic training alone and -0.59% compared with resistance training alone), suggesting concurrent exercise was better than either training mode alone. However, a concern with this later trial was the concurrent group performed twice the exercise volume than either group. As such, it was not clear if the groups would observe similar reductions in HbA1c had aerobic or resistance training increased volume (or time). The HART-D trial,[53] however, was designed to match exercise volume among modalities of exercise (aerobic: 12 kcal/kg/wk at 50-80% VO_2max, resistance: 3 d/wk with 2 sets of 4 upper body exercises, 3 sets of 3 leg exercises, and 2 sets of each abdominal crunches and back extensions, combined: 10 kcal/kg/wk aerobic and 2 sessions of one set one the aforementioned resistance exercises). It was reported

that only concurrent training significantly reduced HbA1c when compared with the control group (-0.34%). This is consistent with the Italian Diabetes and Exercise Study showcasing concurrent exercise is effective at lowering HbA1c, LDL cholesterol, and blood pressure, compared with standard of care.[54] It also corroborates evidence that short-term high functional training (e.g. CrossFit) improved insulin sensitivity and pancreatic function in people with T2D.[30,55] The relationship by which exercise improves pancreatic function is beyond the scope of this review, but increases in GLUT2 transporter content, Akt signaling, and glucokinase activity. Further, mitochondrial function within the beta-cell cell may be involved,[28] and muscles may relase cytokines that influence beta-cell mass and/or function.[56] In either case, these studies align with current ACSM and ADA guidelines recommending concurrent training and the inclusion of at least 2 resistance training days in a week, as part of reaching at least 150 min of moderate intensity exercise to impact glycemia.

High intensity interval training for glycemic control

While the benefit of physical activity/exercise on glycemic control in T2D is established, time constraints are a commonly reported barrier to exercise,[57] as only ~20% of U.S. adults currently meet physical activity guidelines. High-intensity interval training (HIIT) has garnered attention over recent years, providing a time-efficient means of improving glycemic control and cardiovascular health in those with T2D. In comparison to other continuous high intensity exercise options, HIIT was reported may bee enjoyable for some, despite the stronger feeling of fatigue.[58] To this extent, some overuse injuries have been reported during HIIT trials, although HIIT does not appear to place exercisers at greater injury risk than traditional continuous exercise. Rather, as with any exercise program, initial fitness level should be taken into consideration, so exercise acclimation periods are appropriate, and inclusion of warmups and cool-downs are warranted. Thus, for those who are medically cleared for a vigorous exercise program, HIIT can provide benefits as an alternative to traditional, moderate intensity exercise.[59] Additional risk with high intensity training is exercise-related hypoglycemia, particularly among insulin users. Non-insulin (or insulin secretagogue) users on the other hand have minimal risk and would benefit from high intensity training to maintain glycemic status.[81] Importantly though, the long-term utllity and adherence rates of HIIT has not been adequately investigated among people with prediabetes and T2D. Thus, incorporation of HIIT is fair along with continuous exeercise for promoting exercise volume.

Interval training consists of alternating exercise and recovery stages. In HIIT, one may alternate 10 seconds to 4 min of high intensity aerobic exercise (e.g., 75-95% HRmax) with 12 seconds to 5 min of active or passive recovery (e.g., 30-60% HRmax; Table 1). This contrasts with traditional continuous exercise, during which individuals maintain a given intensity for a set period. In fact, high-intensity exercise often elicits a heart rate response around 75-95% HRmax, and current guidelines from ACSM recommend at least 75 min of vigorous activity per week, with no more than 2 consecutive days between bouts of activity. To date, evidence has emerged highlighting HIIT, similar to traditional continuous high intensity exercise, can yield favorable glycemic control. Short-term HIIT consisting of six sessions of 10 × 60-s cycling bouts, each reaching ~90% HRmax, on the cycle ergometer over 2 weeks was shown to decrease average 24 hr blood glucose readings when measured with CGM. Additionally, short-term HIIT training improved mitochondrial capacity measured via muscle biopsies, suggesting that skeletal muscle has greater oxidative capacity to utilize glucose as an energy source.[60] In addition, pancreatic function in response to HIIT was examined in an 8-week cycling intervention in T2D. Participants were placed in a HIIT exercise regimen (3 sessions/wk of 10 × 60-s cycling at ~90% HRmax for 8 weeks). Compared to a matched healthy control group, HIIT reduced fasting glucose concentrations, HbA1c, HOMA-IR (Homeostatic Model of Assessment of Insulin Resistance, a proxy for insulin resistance), and HOMA-b (an index of insulin secretion) as well as abdominal fat mass compared to baseline.[61] In a meta-analysis of ~1400 patients with T2D, HIIT was shown to induce greater benefit to HbA1c, HOMA-IR, fasting serum glucose, and VO_2peak than those exercising at moderate and low intensities.[62] However, the meta-analysis did not compare standardized energy expenditure across the groups, suggesting that groups potentially performed different levels of work that prompted exercise adaptations across intensities.[60] In either case, HIIT over 8 weeks, consisting of 3 sessions/wk of cycling (between 80-110% of peak power output), increased aerobic capacity and reduced blood insulin concentrations and HOMA-IR in adults with T2D, when compared with non-insulin resistance non-obese controls.[63] Together, these findings suggest HITT is an effective program for glycemic control in T2D.

Whether HIIT is better than continuous training remains unclear.[64] When compared with 3 d/wk of continuous endurance training (40 min of cycling at 50% peak workload), HIIT (10, 1-min intervals at 95% peak, interspersed with 1-min active recovery between working intervals) for 11 weeks promoted greater gains in VO_2max but similar benefits in HbA1c, fasting glucose, postprandial glucose, and HOMA-IR in T2D, despite lower total energy expenditure and time requirement.[65] These findings are consistent with a recent meta-analysis identifying 345 patients over 13 HIIT trials in patients with T2D had significant reductions in HbA1c (mean difference: -0.37%), when compared to a non-training control group.[66] Further, no significant differences were found between groups in HOMA-IR or reducing CVD risk. In particular, a HIIT cycling exercise regimen of 1 × 4 min of cycling at 90% peak VO_2peak, 3 sessions/wk for 12 wk, in T2D decreased pulse wave velocity (PWV), a measure of arterial stiffness, as well as improved systolic blood pressure to comparable levels of that of moderate intensity continuous training (MICT).[67] Moreover, flow mediated dilation (FMD), a non-invasive approach to measure endothelial function, had similar benefits between HIIT and MICT in T2D.[68]

While aerobic HIIT has incorporated treadmill vs. cycling modalities, newer work has begun examining the utility of resistance HIIT to foster fitness and glycemia. A year-long trial comparing the effects of moderate intensity to high intensity resistance training found more vascular benefit in those completing resistance HIIT. The HIIT group completed 10-12 repetitions of upper (seated row, seated lat pulldown, seated chest press, and standing shoulder press) and lower limb (less press, one leg lunge, and plank) exercises at 90% HR reserve (HRR), followed by 1 min of resting at 40-60% HRR, for 3 sessions/wk. The MICT group completed continuous cycling at 40-60% HRR. Carotid intima-media thickness (cIMT), a measure used to diagnose the extent of carotid atherosclerotic vascular disease, decreased in both groups, but only HIIT reduced PWV, thereby favoring reduced arterial stiffness.[69] Additional work examining resistance HIIT versus other combinations of continuous or HIIT aerobic training in T2D awaits to be established for maximal glycemic benefit.

Exercise timing relative to daytime and meals

The timing of physical activity/exercise for optimal glycemic control has recently become an area of intense research. Timing of activity implicates both the time of day and before/after meals as being important for long-term glycemic control and postprandial glucose spikes across the day. To identify the best time to exercise, it is worth noting that circadian physiology has underlying influence on glucose homeostasis. Indeed, our body has circadian clocks as evidenced by diurnal oscillations in a variety of physiologic processes that include body temperature, glucose tolerance, circulating insulin, and adipose tissue-related hormones (e.g. adiponectin, leptin, etc.). Interestingly, these processes all tend to collectively be worse in the afternoon/evening compared with morning among healthy individuals.[70] In turn, some reports suggest consuming smaller meals may be beneficial for glycemia next day compared with traditional large dinner meals (e.g.. > 30% total kcals)[69] Furthermore, people with T2D have a disrupted circadian rhythm such that insulin

sensitivity is relatively better in the evening but gets worse throughout sleep and into the morning, thereby raising plasma glucose (often called the dawn phenomena).[71] This circadian misalignment may be improved with exercise, although specific exercise work in T2D is needed. Such diurnal oscillations suggest that glucose metabolism is "better" at specific times during the day, and incorporating exercise based on this timing may result in greater glycemic control. To date, some[71-74] but not all[75,76] research suggest physical activity in the afternoon or evening may be more beneficial for circulating glucose and insulin sensitivity, compared to equivalent physical activities done in the morning in people with and without T2D, on or off insulin therapy. Importantly, not all outcomes seem to respond to afternoon exercise better than morning exercise. In fact, work on body weight and food intake have recently suggested morning exercise is better for weight management as well as activity adherence.[77] Thus, determining the best time of exercise may be outcome dependent. Practically speaking, though, activity should be encouraged whenever the patient is consistently able to fit in their schedule. Indeed, a retrospective cohort study[78] of the National Health and Nutrition Examination Survey (NHANES) reported that physical activity amount, regardless of timing, was associated with lower all-cause mortality in men and women. Thus, considering exercise timing to foster engagement and adherence is seemingly most relevant for glycemic benefit.

It should be noted that several studies have found post-prandial glucose to be a stronger predictor of future CVD than fasting glucose.[79] As a result, it might be appropriate to wonder whether people should exercise before or after a meal to further refine the glycemic response, independent of time of day. This effect could have concomitant benefit on vascular physiology by lowering postprandial glycemia-related endothelial dysfunction and oxidative stress.[80] However, few studies have been conducted on whether fasted states of exercise confer greater glycemic benefit than fed states in people with T2D. A consensus statement from ACSM[81] concluded that current evidence suggests postprandial exercise provides better glucose control by attenuating acute glycemic spikes, regardless of exercise intensity or type, with a longer duration (≥45 min) providing the most consistent benefits.[78] However, it should be mentioned that, of studies, only Francois et al.[82] showed that "exercise snacking" (6 × 1 min intense incline walking at 90% HRmax on a treadmill) 30 min *before a meal* reduced 3-h postprandial blood glucose after breakfast and dinner among patients with T2D or insulin resistance, compared to traditional 30 min moderate-intensity (60% HRmax). Additionally, Edinburgh et al.[83] found that moderate-intensity cycling (60 min performed at 65% VO_2peak for 6 weeks) prior to carbohydrate ingestion improved postprandial insulin sensitivity and reduced insulinemia and lipemia, but not plasma glucose, among overweight/obese men. Other studies showed that brief exercises *after meals* blunted glucose spikes. For instance, these brief exercises included (a) 3 sets of 1-min light intensity jogging + 30 s of rest; total duration of 4 min for each exercise bout, every 30 min throughout the day, 20 times in total; (b) 3 sets of 15 min bouts at 3 METs after a meal[84]; (c) resistance exercise (up to 40% of their bodyweight)[85] (d) 10 × 1 min HIIT (10 × 1 min work-bouts at 95–120% of individual peak power output, separated by 1 min low-intensity cycling)[72]; and (e) 4 bouts including 3 min at 56.5 ± 3.9 % VO_2max after breakfast.[86] Interestingly, postprandial exercise also reduced acute elevations in serum triglyceride levels after high-fat meals and reduced functional derangements from lipid-induced oxidative stress[87-89], suggesting post-meal exercise may benefit both glucose and lipids to support cardiovascular health. Collectively, these findings suggest "exercise desserts" immediately post-meal may yield optimal benefit for attenuating postprandial spikes.

Breaking up sedentary activity with physical activity

Sedentary behavior is now recognized as an independent risk factor for chronic disease. Based on a NHANES analysis, U.S. adults spend nearly 8 hr/d on average being sedentary.[88] Sedentary behavior is generally defined as any waking behavior characterized by a low level of energy expenditure (less than or equal to 1.5 METs) while sitting, reclining, or lying (e.g. TV-watching, screen time).[90,91] This is clinically concerning since high sedentary activity (e.g. generally ≥ 8 hrs) is associated with increased risk of all-cause mortality, cardiovascular disease, and T2D.[92] Remarkably, every 1 hr increase in sedentary activity above 8 hr/d was associated with an 8% increased risk of cardiovascular mortality and 1% increase in risk of T2D.[92] In another cohort, 1 extra hr of sedentary time over an 8 d period was associated with 22% increased odds of T2D adults aged 45-70 yr.[93] Additionally, greater sedentary time was associated with hyperglycemia and incident T2D independent of physical activity levels in a multi-ethnic U.S. population.[94]

Given the alarming public health implications of sedentary activity, independent of physical activity, health professionals and researchers have revised the 2nd edition[95] of the U.S. Physical Activity Guidelines for American to include sedentary activity as an independent risk factor for all-cause and cardiovascular mortality and incident T2D. This recommendation is, in part, based on interventional studies showing benefits in glycemic control upon breaking up sedentary activity and/or replacing sedentary time with light-intensity or moderate-intensity activity. For example, interrupting prolonged sitting with activity breaks, such as light-intensity walking or simple resistance activities (half-squats, calf raises, gluteal contractions, and knee raises) for 3 min every 30 min over 8 hr, decreased postprandial glucose incremental area under the curve by ~14 mmol/h/L among previously inactive adults with T2D.[96] Replacing sitting time with standing (2.5 hr/d) and light-intensity walking (totaling 2.2 hr/d) every 30 min also improved 24hr glucose levels and insulin sensitivity, even more so than structured, moderate-level cycling activity for 1.1 hr/d in individuals with T2D.[97] However, Loh et al.,[98] in a meta-analysis of trials comparing breaking up sedentary activity to continuous sitting to prevent T2D demonstrated only a small decrease in standardized mean plasma glucose for breaking up sedentary activity after matching for energy expenditure. Similarly, the evidence is unclear whether breaks from sitting have clinically relevant impacts on hyperglycemia in free-living environments.[99,100] Interestingly, less-frequent active interruptions (sitting interrupted with 6 min of simple resistance exercises every 60 min) improved acute post-prandial glycemic control post-lunch, while more-frequent interruptions (3 min resistance exercises every 30 min) were more beneficial for nocturnal glucose in those with medication-controlled T2D.[101]

Although less researched, short, high-intensity exercises may also have glycemic control and other cardiometabolic benefits as seen in light- and moderate-intensity exercises. For example, a review on "exercise snacks" (isolated bouts of vigorous exercise lasting ≤1 min)[102] summarized several RCTs describing improvements in cardiorespiratory fitness (e.g. VO_2peak and peak power output).[102-104] The exercise prescriptions for these studies included: 1) three daily bouts of vigorous stair climbing (climbing 60 steps as fast as possible)[105]; 2) three isolated 20-second "all-out" cycling bouts, about 1-4 hr apart daily; 3) stair-based exercise snacks (~15–30 sec)[106]; and 4) 5 × 4-second maximal cycling sprints on a specialized ergometer, once per hour.[107]

In addition to exercises, it is also of interest to investigate the effects of 'domestic' physical activity on glycemic control as domestic chores are the main contributors to total daily physical activity in older patients with T2D.[106] Few studies have been done isolating household activity effects on glycemic control, with even fewer to none among patients with T2D. Li et al.[107] in a cohort study of the UK Biobank among participants without diabetes, reported that replacing 30 min/d of sedentary activity with daily activities (e.g. walking for pleasure, pruning, watering the lawn, weeding, lawn mowing, car maintenance etc.) resulted in a 6-31% risk reduction in T2D. Stair climbing (6 continuous repetitions of climbing to the second floor (21 steps) at a rate of 80-110 steps/min) significantly reduced postprandial glycemia at 150 min post meal compared to resting,[108] but not necessarily 24 hr glucose or long-term hyperglycemia, as evidenced by minimal change in 24 hr glucose comparing 60-sec pulses of vigorous stair-climbing to resting over 6 weeks.[109]

When taking together, it seems reasonable to conclude that interventions breaking up sedentary activity are favorable in at least providing acute glycemic benefit.

Observational and some experimental studies[110-114], but not all,[115,116] on breaks in sedentary time affecting blood pressure and lipid levels have implied similar improvements on other cardiovascular risk factors. For example, Dempsey et al.[114] reported that interrupting sedentary time with brief bouts of walking among patients with T2D produced small yet significant decreases in blood pressure (SBP/DBP: 14±1/8±1 mmHg). Champion et al.,[112] among healthy adults aged 18-55yr, found that sitting time interrupted hourly with 20 min light-intensity treadmill desk walking between 1.2-3.5 km/h acutely reduced plasma glucose, triglycerides, and blood pressure modestly (3-4% decrease). Certainly, more long-term work is needed as well as investigation on other cardiovascular risk factors and measurements in patients with T2D such as blood pressure, LDL cholesterol, endothelial function, coronary artery calcium, and arterial stiffness. Importantly, these breaks in sedentary behavior with physical activity need not be structured exercise sessions (e.g. 30-60 min of moderative vigorous movement), and light-intensity activities (e.g. household activities) and/or resistance exercise may be feasible for impacting cardiometabolic health. Thus, in individuals who are unable to do conventional moderate or vigorous exercise for 150 min/wk or 75 min/wk, respectively, other modes of movement broken up throughout the day may serve as suitable alternatives provided they are done consistently.

Exercise cardiometabolic benefit beyond weight loss

Exercise as a part of lifestyle recommendations promotes weight loss of 5-10%. Yet, many acknowledge that increases in energy expenditure via exercise alone may not induce weight loss if energy intake is not kept constant and/or if alterations in non-exercise physical activity occur such that people sit more. In fact, recent work highlights that despite high energy expenditure from exercise, adaptative thermogenesis (i.e. metabolic adaptation) occurs during weight loss in some people such that their resting metabolism declines, and this makes losing weight and/or maintaining weight loss challenging.[117,118] Thus, it is essential to acknowledge that weight loss is just one measure of T2D and CVD risk reduction that does not exclude other health benefits.

One the main health benefits observed from exercise, independent of weight loss, is the shift in body composition. Specifically, exercise often maintains/increases fat-free mass (e.g. muscle mass) and reduces total body fat and/or visceral fat (VAT). Indeed, a recent meta-analysis[119] revealed that exercise interventions that follow ACSM-based moderate to high intensity exercise (40-90% VO_2max) for 30-60 min/d, showed a marked reduction in total body fat, accompanied with a significant decrease in triglycerides. Others[120] have also showed that high intensity exercise (60-75% VO_2max) for 3-5 d/wk was more effective than continuous moderate exercise in reducing total body fat percent in people with obesity, independent of BMI, along with 17% higher VO_2max. These findings suggest intensity of exercise may be ideal for body fat reduction. In fact, several studies[121-124] report effects of aerobic exercise on reducing VAT, while emphasizing that adherence and intensity of exercise may play a significant role. This is clinically relevant since VAT is the fat deposited around the abdominal organs and is considered tightly associated with insulin resistance, chronic inflammation.[125] hypertension, metabolic syndrome and T2D,[126,127] But, recent work from a large clinical trial demonstrated there is no difference in fat loss when intensity of exercise is matched on energy expenditure,[128] suggesting exercise volume/time is key. Interestingly too this later work shows that aerobic exercise maintains lower body muscle mass, while high intensity plus volumes of exercise may be associated with declines in upper body muscle mass.[128] In turn, resistance exercise is important to consider for increasing fat-free mass specifically.[129] This is consistent with a meta-analysis[122] describing that, compared to strength training, low intensity aerobic exercise, or a combination of both, performed at high volume (>250min/wk) moderate intensity physical activity was associated with significant weight loss including loss in VAT. It is worth noting though that aerobic exercise may be more beneficial on reducing VAT when compared with resistance exercise, although both lower subcutaneous fat.[130] Either way, low impact aerobic exercises, like walking 3 d/wk, can be extremely beneficial for decreasing VAT among women with T2D between 50-70 yr when performed at a 65-70% VO_2max for 50 min.[131] Thus, performing exercise with current ACSM and ADA recommendations seems effective at reducing total body fat and VAT in people with obesity.[132]

Another consideration is that many people with obesity/T2D also develop concurrent non-alcoholic fatty liver disease (NAFLD), characterized by ectopic fat accumulation in the liver. NAFLD is believed to result from overnutrition and lack of exercise, leading to insulin resistance, lipogenesis, and inflammation. People with T2D and NAFLD have exaggerated hyperinsulinemia and dyslipidemia compared to those without NAFLD, signifying that the amount of liver fat is germane towards health. Interestingly, moderate to vigorous intensity aerobic exercise around 150-300 min/wk, including brisk walking and jogging, as well as HIIT training at 80-85% VO_2max 3 d/wk, significantly reduces liver fat and provides hepatoprotective effects. Indeed, increasing physical activity, whether aerobic or resistance based without caloric restriction, reduces liver fat,[132] although aerobic exercise may be more potent.[130] Importantly, though, it has been demonstrated that aerobic exercise at approximately 85% HRmax for 60min/d shifts hepatic fat away from saturated and towards polyunsaturated fat, independent of changes in total weight or liver fat. The shift in liver fat composition is relevant as well since it correlated with whole-body insulin sensitivity.[133] This suggests exercise benefits on the liver occurs well before changes in fat content per se.

Systemic inflammation impairs glucose regulation through, in part, disruption in insulin signaling.[134] Exercise reduces pro-inflammatory cytokines prior to clinically meaningful weight loss[135] and favors secretion of anti-inflammation molecules into the general circulation that are considered “exerkines”.[136] Indeed, exercise, with or without caloric restriction, reduces several pro-inflammatory mediators of dysglycemia (e.g. leptin, feutin-A and CRP).[16,137-139] Furthermore, moderate and short-term HIIT interventions reduce circulating free-fatty acids that are key promoters of not only reduced insulin action but also inflammation.[134] Newer work has also highlighted that acute or short-term exercise may reduce circulating levels of extracellular vesicles (among others; *see review* Chow et al.[136]) in people with obesity[140] or prehypertension[141] to favor cardiometabolic health. When coupled with observations that exercise also increases anti-inflammatory hormones from skeletal muscle, (e.g. IL-6, IL-8, BAIBA, lactate, etc.) adipose tissue (e.g. adiponectin),[16,137] and liver (e.g. follistan) for promotion of cardiometabolic health,[136,142] it is clear exercice has wide ranging benefit beyond that of weight loss.

It is important to acknowledge that exercise is also a valuable tool for emotional and mental health. Many patients with T2D develop depression, possibly due to impact of insulin resistance on reward and learning centers in the brain.[143] Regular engagement in some form of moderate intensity aerobic exercise or exercise ‘snacks’ has been shown to improve mood, reduce anxiety and stress, boost self-esteem, and improve sleep quality and cognition.[144,145] Together, these finding support views that exercise can reduce depression in people with T2D,[146] independent of weight loss, via changes in inflammation.[147]

Perspectives and conclusions

Physical activity and/or exercise is essential to improve glucose levels as well as other cardiometabolic risk factors. Activities that favor glucose reductions include taking breaks between long periods of sitting, scheduling workouts after meals to avoid hyperglycemia, and incorporating some form of aerobic and high-intensity resistance exercise in the week. While it is important to recognize the lack of information

on sex and/or race specific recommendations as well as pediatric decisions for engaging in exercise and physical activity is an area worthy of additional work, habitual exercise is established to increase aerobic and muscular fitness, reduce stress/anxiety,[148] and improve sleep.[149] In addition, exercise also reduces body fat, lipids, and blood pressure. Both aerobic and resistance exercise offer unique opportunities to induce gains in glycemic control. While exercise intensity, volume, and frequency are associated with improved glycemic control, the evidence for the optimal exercise dose for blood glucose remains unclear. The reason for this is multi-level, but matching energy expenditure presents a unique issue. When exercise energy expenditure is matched the difference in intensity is often minimized, suggesting volume per se may be key. This is helpful to consider as a message to patients could focus on time engaged in movement, whether high or low intensity. In addition, people with T2D often take medications when advised to exercise, and work over the last 10y have suggested that pharmacological agents (e.g. metformin, statins, etc.) may oppose exercise benefit.[150] This is consistent with more advanced forms of diabetes having smaller magnitudes of improvement in glycemic related outcomes,[23] although more work is needed in people using insulin therapy. Regardless, accumulating 150 min/wk of moderate to vigorous physical activity over 3-5 days (aerobic plus resistance exercise) is beneficial for cardiometabolic risk factor reduction. Performing these exercise bouts in 30-60 minute blocks throughout the week is fair, but it is worth noting that breaking up sedentary behavior with smaller bouts hourly (e.g. up to 3 min or 250 steps/hr) or a few times throughout the day (e.g. 3 x 10-15 min) may be equally effective for glycemia, particularly after meals.[71] At the same time, if a single bout of exercise is performed, newer work highlights that doing it in the afternoon compared to the morning may provide better results due to circadian alignment, although randomized clinical trials designed to impact glucose tolerance/insulin sensitivity are needed. While some of these exercise/physical activity efforts may not yield changes in body weight over time, exercise trials demonstrate health benefits that extend beyond weight loss such as reductions in visceral fat, liver fat, and systemic inflammation as well as memory and sleep. Therefore, physicians and healthcare providers should encourage exercise and physical activity as a tool to improve/manage glycemia, independent of weight loss, for enhanced health and wellness.

Declaration of Competing Interests

We declare no competing interests.

Author contributions

All authors contributed equally to writing, editing, and reviewing this manuscript.

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