Exercise, Pharmaceutical Therapies and Type 2 Diabetes: Looking beyond Glycemic Control to Whole Body Health and Function

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Abstract

Exercise is a powerful therapy for improving glycemic control and increasing cardiorespiratory fitness in adults with type 2 diabetes mellitus (T2DM). However, there is a dearth of evidence investigating interactions or synergies between exercise and most pharmaceutical therapies. This is important as exercise is rarely prescribed in isolation of other background medications used to manage T2DM. Therefore understanding which exercise and drug combinations optimize or blunt responses is crucial. This narrative review discusses advances in weight loss management in diabetes and highlights research opportunities and challenges for combining exercise therapies with newer generations of glucose-lowering therapies with weight loss effects, particularly glucagon-like peptide-1 receptor agonists (GLP-1RAs) and sodium-glucose cotransporter 2 inhibitors (SGLT2is). We discuss the role of exercise in preserving lean mass and increasing physical function along with other potential areas of synergy. We conclude that until the evidence base investigating areas of interaction or synergy between exercise and other glucose-lowering or weight loss therapies is developed, exercise will remain a generic rather than a tailored therapy in the management of T2DM.

Keywords: exercise; type 2 diabetes; glucose-lowering therapies; weight loss; physical function

Introduction

Type 2 diabetes mellitus (T2DM) is a disease characterized by hyperglycemia, resulting from the combination of insulin resistance, impaired insulin secretion, and excessive or inappropriate glucagon secretion. As such, management pathways have historically focused on glycemic control as the key clinical indicator of therapy effectiveness to slow disease progression. This includes exercise as a therapy in the management of T2DM, where numerous studies and meta-analyses have consistently shown clinically meaningful improvements in glucose control following structured exercise training programs1-5. Therefore, exercise interventions or those that promote increased physical activity are a cornerstone of lifestyle therapy options in the management of T2DM.

Overweight and obesity have long been recognized as leading risk factors for T2DM, being present in over 80% of all individuals with T2DM7. Therefore, the management of obesity has become an integral component in the prevention and management of T2DM. However, very little is known about the interaction of exercise and other available therapies used to manage T2DM and obesity (i.e., novel dietary interventions...
and glucose-lowering therapies). This constitutes an important research focus, particularly given the increasing knowledge about the whole body effects of T2DM on far-reaching clinical outcomes.

**Advances to diabetes management—focus on weight loss**

Recent evidence has shown that very low energy diets capable of eliciting substantial amounts of weight loss can lead to the remission of T2DM. The seminal DiRECT trial demonstrated that a meal replacement low energy diet (about 850 kcal/d), followed by transition back to a food-based maintenance diet, led to over 40% remission of T2DM at one year and more than 30% at two years. The high rates of T2DM remission mirror those achieved through bariatric surgery and exceed less restrictive approaches to weight loss. These impressive results have led to an ongoing pilot by the National Health Service (NHS) in the UK for prescribing a meal replacement diet as part of routine care for T2DM management. Along with novel approaches to dietary interventions, newer generations of glucose-lowering therapies have been developed that exert potent weight-lowering properties alongside improved glycemic control. Most notably, glucagon-like peptide-1 receptor agonists (GLP-1RAs) and sodium-glucose cotransporter 2 inhibitors (SGLT2is) are now internationally recommended as second-line pharmacological therapies after metformin, alongside ongoing lifestyle management. Each is particularly recommended for certain sub-groups of individuals including those in whom, in addition to glucose-lowering, there is a compelling need to reduce body weight. As such, the GLP-1RA liraglutide has gained an independent license (at a higher dose of 3 mg) for use in obesity management. Importantly, the glucose-dependent mechanisms of action of GLP-1RAs and SGLT2is therapies mean that their beneficial effects come with low risk of hypoglycemia, particularly when used without sulphonylureas or insulin. The STEP trials investigating the efficacy of semaglutide in the management of obesity are set to further revolutionize the use of GLP-1 receptor agonists as a weight loss agent. Their effects also extend beyond weight loss and glycemic control, as large cardiovascular outcome trials have demonstrated that several GLP-1RAs therapies elicit compelling cardiovascular protection in the form of reduced risk of major adverse cardiovascular events. Similarly, a number of SGLT2is therapies have also shown cardiovascular benefits, including reduced hospitalization for heart failure. As a result of these recent developments, there is now an expanded arsenal of dietary and non-dietary therapies at the clinician’s disposal in the routine management of T2DM, obesity and other comorbidities.

**Is weight loss always desirable? Consideration of lean mass and frailty**

The combination of weight loss and improved glycemic control associated with novel dietary interventions and newer pharmacological therapies is appealing, particularly given their independent associations with a plethora of co-morbidities. However, it is also important to understand the impact of these therapies on other important markers of health, particularly physical function, frailty and body composition. T2DM is not just a disease of the cardiometabolic system, but also reflects a powerful physiological model of accelerated biological aging impacting whole body health and function. As a result, one of the most pernicious sequela of T2DM is an increased risk of poor physical function and frailty. Figure 1 displays the definition and natural history of different stages of frailty, along with its associated clinical and societal impact. Those with diabetes are up to five times more likely to be frail than individuals without diabetes, with frailty and the preceding ‘pre-frail’ state substantially and progressively increasing both the individual [hospitalization, institutionalization and (or) death] and public health (health care expenditure) burden of T2DM. The importance of frailty in the management of T2DM is increasingly recognized and highlighted in two national and international expert consensus statements, calling to have frailty status at the center of treatment decision-making (Fig. 1).

In contrast to a more traditional connotation of the ‘frail’ individual, frailty in T2DM occurs within the context of obesity and is characterized by reduced performance in functional tasks of daily living. Indeed, the ability of those with T2DM to carry out key functional tasks, such as chair sit to stand tasks and handgrip strength, has been shown to be similar to those without diabetes over a decade older. It has been further suggested that the risk of sarcopenic obesity is also increased with T2DM.

The coexistence of obesity and low physical function in T2DM represents an important clinical challenge. On the one hand, diet-induced weight loss may improve physical function, by reducing the biomechanical burden of moving around. On the other hand, it may in fact counter or attenuate positive longer-term prognoses. This is because for every kilogram lost through a hypoenergetic diet, around 25%–30% is due to reductions in lean body mass (predominantly skeletal muscle). Evidence from the LookAHEAD trial suggested that this effect may be even more pronounced in T2DM, where over an 8 year period both the control and intensive weight loss intervention groups lost over 2 kg of lean mass, representing over 90% and 50% of total weight loss in the control and intervention groups, respectively. Similarly high rates of lean mass loss have...
Muscle mass is critical to maintaining healthy human physiology, fundamentally providing the dynamic biomechanical device needed for locomotion and the completion of essential daily activities. It also plays a fundamental role in maintaining cellular homeostasis through contributing to a wide range of physiological processes, including regulating glucose, inflammation, hormonal and energy balance. The loss of lean mass and strength is one of the most consistent hallmarks of aging. Weight-stable adults have been shown to lose an average of 1.5 kg in lean mass per decade, with another study reporting a loss of between 1 and 1.5 kg in inactive men and women older than 45 years over an eight year period. Therefore, as little as a 1 kg loss in lean mass equates to between 6 to 8 years of aging. Another study reported that any leg or appendicular lean mass loss in older men and women is associated with over twice the risk of disability compared to those without lean mass loss. Indeed, in older adults the loss in lean mass contributes to a loss in strength of around 3%–4% per year in men and 2.5%–3% per year in women. Each 1 kg loss in lean mass has also been associated with a 4% higher risk of mortality in older men and 9% higher risk in older women.

It is also apparent that whilst weight loss reduces the mechanical load of locomotion, it does little to improve underlying muscle physiology, with some evidence suggesting that relative aerobic capacity, measured as oxygen uptake per kilogram of lean mass, may actually be modestly reduced with weight loss. It is important to not only consider the absolute mass of skeletal muscle, but also the improvement of muscular function (strength, endurance, flexibility) in order to improve physical function and performance in tasks of daily living. More broadly, weight loss without addressing physical function or the preservation of lean mass may limit the magnitude of longer-term benefits achieved with weight loss alone and leave those with T2DM remaining at an increased risk of poor physical function, sarcopenia and frailty. Therefore, preservation of lean mass is a vital consideration when weight loss is the therapeutic goal or concomitant effect in the management of T2DM.

Frailty definitions, trajectory and impact on type 2 diabetes management

Frailty and diabetes: Factors related to diabetes (insulin resistance, inflammation) greatly increase the risk of pre-frailty or frailty coexisting with obesity. Those with diabetes have been shown to have up to 5 times the risk of frailty compared to those without diabetes. The below treatment algorithm has been proposed by experts in diabetes frailty.
The role of exercise

The importance of poor physical function, sarcopenia and frailty, lies within the fact that they are ‘pre-disabling’ conditions that are suitable for therapeutic intervention. Combined aerobic and anaerobic exercise training provides a powerful anabolic stimulus that improves muscle quality and muscle strength, increases muscle mass and enhances physical fitness and function, with whole body effects that remain unrivalled by any other lifestyle or pharmaceutical intervention. Improved physical function and enhanced performance in tasks of daily living, may also mediate improvements in quality of life.

Previous studies in individuals with obesity have demonstrated that multimodal exercise can be used to help preserve lean mass during a diet-induced weight loss intervention, whilst acting to increase cardiorespiratory fitness and improve physical function (Table 1). However, much less is known about the generalizability of these findings to T2DM. Whilst exercise training has been shown to improve glycemic control and fitness in T2DM, the effect on lean mass is more equivocal, with a lack of evidence investigating whether the loss of lean mass with energy restriction can be attenuated with exercise training. This lack of evidence is important, as it is known that cardiorespiratory fitness, muscle quality and function are impaired in T2DM, hence it cannot be assumed that the anabolic effects of high intensity or resistance exercise observed in healthy individuals can be generalizable to T2DM.

It is also important to recognize that the vast majority of the evidence underpinning the efficacy of exercise in T2DM is derived from interventions involving moderate- to vigorous-intensity aerobic exercise or resistance training, based on traditional guidelines. However, over recent years there has been an expansion in guidelines to incorporate the full physical activity intensity spectrum, both for the general population and those with T2DM. Whilst traditional guidance to achieve at least 150 min of moderate-intensity physical activity and under-take two sessions of resistance exercise remains the bedrock of newer physical activity guidelines, there is also an increasing recognition that reducing sedentary behavior (in particular prolonged sitting time) and increasing light-intensity physical activity can have important effects on cardiometabolic health; at the other end of the spectrum, vigorous-intensity exercise can be undertaken using different approaches, including the use of near maximal exercise through interval training. Table 2 details the key definitions and how these relate to current guidelines for T2DM. There is a need to investigate how application of the full physical activity intensity spectrum can be optimized for the promotion of improved physical function. For example, mounting observational evidence suggests that sitting per se can exacerbate the symptoms of frailty and impaired physical function and that replacing sitting with light movement (e.g. standing and slow upright movement) is associated with better physical function. Moreover, high-intensity interval training elicits improvements in body composition (fat to lean mass ratio) and muscle function (strength and power). In some instances, the improvement in certain outcomes (quality of life, exercise capacity and mitochondrial function) may be greater than those achieved through moderate-intensity continuous training.

Possible interactions and synergies

Whilst there has been extensive research into the effects of exercise training or behavioral physical activity interventions on insulin resistance and glycemic control in T2DM, much less research has actively considered how exercise can be combined to add synergy to pharmaceutical or dietary interventions delivered through routine care. Metformin provides a cautionary tale and demonstrates the need for this research to be undertaken. It is well established that exercise and metformin independently elicit positive effects on the improvement of whole body and peripheral insulin sensitivity. However, there is a growing body of evidence suggesting that an antagonistic interaction exists between the two therapies. More specifically, metformin has been shown to attenuate exercise-induced improvements in peripheral insulin sensitivity (30%–50%), blunt favourable effects of exercise on cardiovascular risk factors (such as blood pressure and inflammation), lower aerobic capacity, and blunt hypertrophic responses to exercise.

Previous research has also proposed a juxtaposition of exercise and metformin, at the level of mitochondria. For example, a typical physiological response to meet the energy demands of exercise training involves increasing biogenesis and mitochondrial respiration at the site of skeletal muscle. However, when combined with metformin treatment the outcomes are less pronounced (coupled with significant heterogeneity), which may...
be driven by the inhibition of mitochondrial respiration\textsuperscript{82}. The timing of exercise and metformin administration may also be an important modifiable factor that influences glycemic control. For example, preliminary evidence suggests that exercising at 30 min post-breakfast (which was combined with metformin), stabilizes postprandial glucose fluctuations and leads to the largest reductions in postprandial glucose compared to exercise undertaken later in the post-breakfast period\textsuperscript{83}.

These results demonstrate that the combination of exercise with pharmacotherapy does not necessarily result in added-value over either therapy alone, with the alternative also possible that the effect of one may actually work to blunt the effect of the other. However, the clinician is left with a lack of evidence when deciding how best to combine glucose-lowering agents with exercise for the optimization of diabetes management. This lack of knowledge extends to possible synergies or interaction with newer classes of glucose-lowering medications shown to result in clinically meaningful weight loss as well as glycemic and cardiovascular benefits. To date only two small studies have examined the combined effects of a GLP-1RA (liraglutide) or SGLT2i (dapagliflozin) with exercise training on body composition and fitness\textsuperscript{83,84}. Whilst both trials prescribed a minimum of three 60-min supervised sessions per week (ranging from 65%–85% heart rate reserve), only one included a session specifically dedicated to resistance exercise (3 sets of 12 repetitions with 30 to 45 s rests between 2 sets)\textsuperscript{84}. Interes-

Table 2  Physical activity guidelines for patients with type 2 diabetes and the corresponding exercise intensity (where appropriate)

| ADA Guidelines for adults with type 2 diabetes\textsuperscript{a} | % VO\textsubscript{2} peak or % 1-RM\textsuperscript{b} | % HR max | Borg rating of perceived exertion (RPE)\textsuperscript{c} | METS | Examples |
|---|---|---|---|---|---|
| Moderate-intensity exercise | A minimum of 150 min per week, not allowing more than 2 d to elapse between exercise sessions. | 46–63 | 64–76 | 12–13 | ≥3, < 6 |
| Vigorous-intensity exercise | Potential to be used as an alternative to moderate-intensity aerobic exercise provided a minimum of 75 min per week is undertaken. | 64–90 | 77–95 | 14–17 | ≥6 |
| Near-maximal to supra-maximal | ≥91 | ≥96 | ≥18 | | Cycling/running intervals at maximal effort |
| Light-intensity physical activity | Increasing active tasks of daily living should be recommended to all. This intensity of exercise may also be used as the initial focus or as an introduction to exercise in previously inactive individuals. | 37–40 | 57–63 | 9–11 | ≥1.5, < 3 |
| Resistance exercise | 2–3 sessions per week performed on non-consecutive days, with 8–10 exercises per session. 1–3 sets of each exercise should be performed, reaching ‘near-fatigue’ by the end of each set. | 40–60 | – | 13–15 | ≥3 |
| Sedentary behavior | All patients should reduce their daily levels of sedentary behavior. In particular, prolonged sitting should be interrupted regularly with either light or moderate activity. | – | – | – | <1.5 |

\textsuperscript{a} adapted from reference 6; \textsuperscript{b} adapted from reference 60; \textsuperscript{c} adapted from reference 67. % VO\textsubscript{2} peak: percentage of peak oxygen consumption; % HR max: percentage maximal heart rate; RPE: rating of perceived exertion; % 1-RM: percentage of 1-repetition maximum; METS: metabolic equivalents.
tingly, both trials demonstrated the potential preservation of lean mass with weight loss and increases in cardiorespiratory fitness. The magnitude of increases in fitness suggests that whilst the co-administration of a GLP1-RA or SGLT2i therapy with exercise training does not augment increases in fitness compared to exercise alone, it does not appear to attenuate them. Evidence is more mixed and contradictory for other health effects, with the combination of an SGLT2i and exercise potentially working together to blunt the effects on insulin sensitivity compared to exercise alone, whereas the opposite was found for exercise combined with a GLP-1RA.

In contrast, the combination of SGLT2i and exercise has been shown to enhance effects on left ventricular filling pressure and right ventricular systolic pressure, whereas the combination of exercise and GLP-1RA has been suggested to blunt responses in diastolic function.

In addition to the focus on lean mass preservation and fitness, GLP-1RA therapies also hold promise for potentiating the beneficial effects of exercise training on the microvasculature. Decreased microvascular blood flow and impaired mitochondrial function observed with insulin resistance is one of the mechanisms linked to lower levels of cardiorespiratory fitness and muscle dysfunction in T2DM. Animal models have suggested this could be due to the impaired insulin regulation of nitric oxide synthase (NOS). GLP-1 has been shown to stimulate NOS through insulin independent pathways and cyclic AMP via G-protein–coupled receptor signalling, leading to vasodilation and increases in muscle perfusion and oxygenation. These findings are supported by human studies where the prescription of GLP-1RA has been shown to result in increased physical fitness and function within clinical populations supporting possible independent effects at the microvascular level. Early evidence from animal models has further suggested that GLP-1RA therapies may act to restore exercise-mediated vascular mitochondrial response in models of insulin resistance. The intriguing hypothesis that GLP-1RA may lead to improved microvascular function that may potentiate the effects of exercise within T2DM needs to be investigated in humans.

The sparse knowledge of the interactions or synergies between exercise and pharmaceutical therapies is also matched with limited knowledge in dietary weight loss interventions in diabetes, particularly low energy diets designed for T2DM remission. In a recent head-to-head trial of a low-energy diet vs. exercise training, the dietary intervention led to T2DM remission in over 80% of cases, whereas there was no change in MRI assessed diastolic function or cardiorespiratory fitness. In contrast, exercise training had little impact on weight loss, but did improve markers of glycemia (fasting insulin and glucose), diastolic function and exercise tolerance. However, these interventions were not combined.

### Safety considerations

For the large majority of people, including those with T2DM, exercise is a valuable therapeutic aid which can help promote health and well-being. Although the risk of cardiovascular events is transiently increased during exercise, with the risk greatest for sedentary individuals undertaking an acute bout of vigorous-intensity exercise, the absolute risk remains low, including in individuals with coronary heart disease where the rates of cardiac arrest, acute myocardial infarction (MI), and cardiac death have been reported at less than 10 events per 1,000,000 patient-hours of exercise training.

However, the management and sequelae of T2DM does require the need for specific considerations. Those taking insulin or insulin secretagogues have a higher risk of developing exercise induced hypoglycemia. This may be a significant barrier to engaging in physical activity for this group of people. As the hormones released during exercise result in some of the same symptoms as hypoglycemia (i.e., sweating, dizziness and tiredness), this can make it difficult to differentiate between the onset of hypoglycemia and the normal physical sensations associated with exercise. Other safety concerns to exercise include the fact that poor blood glucose control and neuropathy may lead to impaired cutaneous blood flow and sweating, potentially leading to sub-optimal core temperature regulation in hot weather, or the need to reduce weight-bearing activity and pressure with foot ulcers. Implementing of appropriate precautions including changes to medication regimens, timing and macronutrient composition of food and the timing and type of activity, appropriate clothing and footwear, along with regular monitoring of blood glucose before, during and after exercise should effectively minimize the risk of hypoglycemia or hyperglycemia and other adverse events.

The use of newer generations of medications for T2DM discussed in this article may also have some specific considerations that require further investigation. For example, it has been suggested that SGLT2i therapies may lower resting heart rate in those with higher baseline heart rates (>70 bpm), potentially driven by decreased sympathetic activation, whereas GLP-1RAs act to increase heart rate. These effects may have implications for exercise tolerance or prescriptions based on heart rate reserve. Moreover, the decreased carbohydrate availability may mean that participants are likely to report higher ratings of perceived exertion during exercise as has been seen in the early stages of a low-carbohydrate diet.

Given that administration of SGLT2i therapies elicits glycosuria, the ensuing osmotic diuresis means that dehydration may also become a concern, with renal blood flow during exercise reduced to 25% of total blood volume at rest. This sympathetically induced renal vasoconstriction may also be related to...
the intensity of the exercise. This also raises the possibility of euglycemic diabetic ketoacidosis, driven by a decreased insulin to glucagon ratio, which induces lipolysis and thereby ketogenesis\textsuperscript{102}. Although rare, there has been some evidence that the occurrence of some diabetic ketoacidosis events with SGLT2i has been proceeded by physical exertion or exercise which warrants further investigation\textsuperscript{103}.

Future directions and research opportunities

The themes highlighted in this article suggest that routine management pathways are a crucial component when considering the efficacy or effectiveness of exercise interventions in the management of T2DM. In particular, exercise is rarely prescribed alone, but in administration with other glucose-lowering agents, with newer generations of medications also having weight loss effects. There is an unmet research and clinical need to ensure that potential interactions and synergies between pharmaceutical and exercise therapies are clearly elucidated, particularly on whole body and cardiometabolic health, substrate utilization, exercise capacity and safety profile. Further research is also required to investigate the extent to which exercise can be combined with a very low-energy diet in the preservation of lean mass, whole body and cardiovascular health and longer-term weight loss. Given the known sex and ethnicity differences in body composition and the whole body effects of exercise including resting metabolic rate, homeostatic control and substrate metabolism\textsuperscript{104,105}, there is also a need to explore whether men and women or individuals of different ethnicity respond differently to the combination of exercise and dietary interventions or glucose-lowering therapies. Age is another potential consideration. Although randomized trials evaluating exercise interventions in adolescents with T2DM are limited and often inconclusive, the recommendations are similar to the general population\textsuperscript{6}. However, as prevalence of T2DM is increasing in younger populations with a concomitant use of glucose-lowering medication, including unlicensed usage in children\textsuperscript{106}, the effectiveness and safety of different therapies when coupled with exercise is unknown in children or younger adults. This is an important research gap as the phenotype of T2DM is often more extreme in younger adults or children than it is in older adults\textsuperscript{107}, which may act to magnify interactions or synergies between different therapies.

Within these wider questions related to the coadministration of pharmaceutical or dietary interventions with exercise, there remains a need to consider more traditional areas of exercise physiology. For example, how does the effect of exercise itself differ depending on the overall dose, intensity or mode in the context of the full physical activity-intensity continuum, from light-intensity physical activity to high-intensity interval training.

Conclusion

Exercise as a therapy for promoting glycemic control and fitness in T2DM has been well established through several decades of research. We argue that there is limited benefit in continuing to replicate these observations. Rather, it is important to consider that exercise is prescribed within the wider management of T2DM, and as such greater focus is needed on how the powerful physiological stimulus of exercise interacts with or adds synergy to glucose-lowering therapies. When exercise is prioritized by the patient or prescribed by the physician, how should the background medication regimen be tailored to potentiate rather than blunt the effects of exercise? Alternatively, how can exercise be used by the patient or physician to enhance the efficacy and whole body response to newer classes of glucose-lowering therapies as they are prescribed? Until the evidence base addressing these questions is developed, exercise will remain a generic rather than a tailored therapy in the management of T2DM.

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