Exercise and Type 2 diabetes: the metabolic benefits and challenges

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Practice Points

- Despite the known benefits of exercise there is a need to develop a personalized approach to optimize the therapeutic effects of exercise prescription. This should cater for the duration of diabetes, glycemic control, lifestyle habits, body fat, initial fitness and complications.

- Reducing sedentary time could be an important alternative to formalized exercise prescription. This takes the focus away from specific intensity, duration and frequency recommendations. The development of accurate monitors to objectively measure spontaneous physical activity and energy expenditure are required to create personalized daily recommendations.

- Diabetes specific exercise programs need to be more widely available and accessible. One of the major barriers is the assessment of cardiovascular risk prior to and during an exercise program. A validated, reliable, submaximal assessment should be developed to increase mass participation in appropriate programs.

- The development of a community based exercise specialist qualification in Europe would increase the availability and effectiveness of programs as well as optimize the impact on patient health.

SUMMARY Regular exercise is known to decrease the risk of all-cause mortality, improve insulin sensitivity and decrease blood glucose in patients with Type 2 diabetes. These improvements have been associated with increased skeletal muscle glucose disposal and a decreased hepatic glucose production. In recent times exercise has been linked to improved cognitive function and a reduced risk of dementia. In addition, the changes in hepatic gene expression are very rapid and suggest a direct impact of exercise. Therefore, the benefits of exercise may be more wide ranging than previously believed. Despite the known benefits it has been a challenge to influence policy makers to incorporate exercise into the management of Type 2 diabetes. This is partly owing to a lack of randomized controlled trials to determine the optimal exercise prescription and the variability in study design. In order to affect an increase in daily physical activity there is a need to develop new screening and monitoring tools to provide individual guidelines.

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The second half of the 20th century witnessed a dramatic increase in the incidence of Type 2 diabetes. It is anticipated that the worldwide prevalence of diabetes will be 300 million by 2025, an exponential increase on the 30 million estimated by the WHO in 1985 [1,2]. During this brief period of time there have been tremendous technological developments that have dramatically changed our lifestyles. In particular it has become clear that decreased daily physical activity is significantly impacting on metabolic regulation. It has been argued that the human genome has evolved to support physical activity and that muscle contraction stimulates the expression of genes responsible for glucose transport, lipid oxidation and mitochondrial biogenesis. The absence of a mechanical stimulus, by exercise, not only decreases energy expenditure but also the expression of these metabolic genes. The consequences of these changes can be directly related to the defects leading to metabolic dysfunction, obesity and Type 2 diabetes [3]. In this context exercise not only provides a valuable preventive and therapeutic strategy for Type 2 diabetes but also a unique model to study the mechanisms of metabolic disease.

Etiology of Type 2 diabetes
The development of Type 2 diabetes is associated with a gradual deterioration in insulin action and insulin secretion [4–6]. A decrease in insulin-stimulated glucose disposal as well as increased hepatic glucose production and adipose tissue lipolysis are the consequences of these metabolic alterations. Normal glycemia can be maintained if the pancreatic β-cells compensate by increasing insulin secretion, but those who develop impaired glucose tolerance (IGT) or Type 2 diabetes fail to produce an adequate insulin response [5–8]. The net outcome of insulin resistance and insulin secretory dysfunction is an increase in the fasting and postprandial glucose concentrations.

A common characteristic of this multitissue metabolic dysfunction is the accumulation of intracellular lipid and/or a decrease in lipid turnover [9]. This is a result of chronic energy imbalance that leads to an increase in adipose tissue mass and circulating nonesterified fatty acids (NEFA) through de novo lipogenesis and decreased insulin suppression of lipolysis [10–12]. A short-term increase in circulating NEFAs by intralipid infusion results in a decrease in whole-body glucose disposal [13–15], an increase in gluconeogenesis [16,17] and a decreased capacity to suppress glycogenolysis, leading to increased hepatic glucose production [17,18]. In addition, elevated NEFAs impair glucose-stimulated insulin secretion in IGT and Type 2 diabetes but not those with normal glucose tolerance [17,19]. However, these metabolic disturbances do not occur when circulating NEFAs are suppressed by acipimox [20,21].

The accumulation of intracellular lipid may not be attributed solely to excess lipid availability but also a decrease in the capacity for substrate oxidation. The number and size of mitochondria are decreased in the skeletal muscle of patients with Type 2 diabetes and long chain fatty acid transport across the mitochondrial membrane is decreased [22]. The nonoxidative metabolism of intracellular triglycerides and their subsequent cytosolic accumulation leads to the generation of lipid intermediaries such as diacylglycerol and ceramides. Both of these have been shown to activate intracellular signaling cascades and impair insulin signaling [9].

Other factors have also been shown to influence insulin sensitivity including adipokines, myokines and inflammation markers to name but a few [23]. A review of these areas is beyond the scope of this article but an emerging area worthy of mention is the potential contribution of neurological impairment to the development of diabetes. There is evidence that dementia is more prevalent in patients with Type 2 diabetes indicating a relationship between metabolism and nervous system function [24]. Koch et al. have shown, using whole body and peripheral insulin receptor knockout mice, that central insulin action is involved in the regulation of glucose metabolism and white adipose tissue mass [25]. Tschritter et al. have subsequently shown that the cerebrocortical response to hyperinsulinemia is reduced in overweight insulin resistant subjects [26]. There is also evidence that circulating lipids can be sensed by the hypothalamus, and given the importance of this gland to the regulation of energy balance, it is plausible that neuronal insulin resistance may contribute to the development and progression of Type 2 diabetes [27]. It remains to be determined if metabolic dysfunction in cells of the nervous system contributes to the development of Type 2 diabetes and to what extent diabetes contributes to impairment of nervous system function.
Exercise & Type 2 diabetes

Physical inactivity is recognized as an independent risk factor for more than 25 chronic diseases, including Type 2 diabetes [3], and is defined as all movement accumulated during the day. For the purposes of this article, exercise is defined as any structured activity designed to investigate clinical or physiologic responses. A low level of physical fitness, as a result of physical inactivity, is associated with a twofold adjusted risk for all-cause mortality in men with Type 2 diabetes [28]. The relationship between fitness and mortality has also been shown in healthy and obese adults [29–31], while other data shows an increased prevalence of cardiovascular risk factors in obese adults and adolescents compared with lean subjects [32]. These associations persist after adjustment for BMI, waist circumference and body fat [30,31]. However, some studies report changes in daily physical activity rather than changes in aerobic fitness or strength. Physical activity is usually quantified by questionnaire or pedometer/accelerometer. While these measures are easier to implement, the subjective reporting by questionnaire and the crude estimates of activity have made it more difficult to interpret the impact of activity on metabolic health. If daily physical activity is to be used to assess the risk of developing Type 2 diabetes or to predict all-cause mortality, then more objective and accurate assessment tools need to be developed. In addition, these tools need to reflect biologically relevant outcomes such as energy expenditure, as will be discussed later.

A meta-analysis of structured exercise training on physical fitness report an 11% increase in maximal oxygen uptake in patients with Type 2 diabetes compared with a 1% decrease in non-exercise controls [33]. On average patients exercised for 49 min, 3.4 times per week for 20 weeks with a broad range of exercise intensities. The analysis revealed that studies adopting higher exercise intensities tended to produce greater increases in physical fitness. Exercise training is known to improve insulin sensitivity [34], glucose tolerance [35] and glycemic control [33] while decreasing fasting insulin concentrations [36]. There are also additional lipid lowering [37], antihypertensive [38], vascular [39] and body mass benefits [40] associated with chronic exercise training. Therefore, exercise has the potential not only to be an effective treatment for Type 2 diabetes but also to reduce the morbidity and mortality associated with the disease.

The benefits of exercise for patients with Type 2 diabetes

- Glycemic control & insulin sensitivity

There have been a number of recently published randomized controlled trials assessing the impact of exercise/lifestyle intervention on glycemic control [41–44]. The Italian Diabetes and Exercise Study (IDES) [41] and the Look Action for Health in Diabetes (AHEAD) trial [43] compare standard care with a lifestyle intervention combining exercise and dietary restriction. The IDES found a -0.42% reduction in glycosylated hemoglobin (HbA1c) after 12 months [41] and the Look AHEAD trial report a similar decrease (-0.36%) after 4 years [43]. The benefits of aerobic exercise, resistance training and combined aerobic and resistance exercise on glycemic control has been investigated by the Diabetes Aerobic and Resistance Exercise (DARE) [44] and Health Benefits of Aerobic and Resistance Training in Individuals with Type 2 Diabetes (HART-D) [42] studies. Both studies found that combined aerobic and resistance exercise improved glycemic control. The DARE study found that aerobic exercise and resistance training alone also improved glycemic control but the HART-D study only found an improvement with aerobic training in patients with an initial HbA1c greater than 7%.

Given the importance of exercise training in the management of Type 2 diabetes, the literature contains relatively few randomized controlled trials and there is a high degree of variability in the mode, duration and intensity of exercise training. Despite these difficulties the results from meta-analyses and systematic reviews consistently report a reduction in glycosylated hemoglobin. Boule et al. examined 12 aerobic training studies and two resistance training studies that compared an exercise training group to a non-exercise control group [33]. The aerobic training groups exercised 3.4 ± 0.9 times per week for 18 ± 15 weeks. The resistance exercise groups trained 2.5 ± 0.4 times per week (2.5 ± 0.7 sets of 10.0 ± 0.7 exercises with 13 ± 7 repetitions) for 15 ± 10 weeks. The weighted mean post intervention HbA1c was -0.66% lower in the trained versus control groups. There was no significant reduction in body mass following any of these interventions indicating that HbA1c can be improved by exercise independent of weight loss.

These results are similar to those of Thomas et al. who report a 0.6% reduction in HbA1c in their meta-analysis of 13 randomized
controlled trials involving 361 participants [45]. The trials lasted from 8 weeks to 1 year and comprised resistance exercise, aerobic exercise or both. The analysis also demonstrated that HbA1c had decreased 0.8% in exercise trials less than 3 months and 0.7% following interventions less than 6 months in duration. Short-duration trials often have more supervised sessions and individual prescriptions and may therefore influence the outcome of these trials. It may also be that compliance is greater in short-term interventions but more difficult with increasing duration.

The improvement in glycemic control is attributed to improved glucose tolerance and insulin sensitivity following exercise training. Holloszy et al. normalized or improved glucose tolerance in a group of patients with Type 2 diabetes or those with IGT following a 12-month exercise training program [35]. Perseghin et al. have shown improved insulin sensitivity in the insulin resistant offspring of Type 2 diabetes parents after a 6 week aerobic training program [46], while others have shown that 7 days [47,48] or even a single bout of exercise [49–52] improved glucose tolerance and insulin sensitivity in healthy and insulin-resistant individuals. These changes, especially in response to acute or short-term exercise are independent of improvements in oxygen consumption, blood flow or weight reduction indicating that local changes regulate the improvements in glucose uptake and utilization. The training related benefits of exercise can also diminish relatively quickly. Hortobagyi et al. reported decreased insulin sensitivity in exercise trained endurance athletes following 14 days of training cessation [53]. Heath et al. found a similar result in active men and women following 10 days of detraining, but found that glucose tolerance could be restored following an acute bout of exercise [54].

### Skeletal muscle glucose disposal & gene expression

The synergistic effect of exercise and insulin on whole body glucose disposal led to the speculation that exercise and insulin may have distinct mechanisms promoting glucose transport [55]. Skeletal muscle accounts for 80% of insulin-mediated glucose disposal and has been the focus of mechanistic studies. Insulin-stimulated and contraction-mediated glucose transport requires the translocation of GLUT-4-containing vesicles to the plasma membrane but the signaling cascades are distinct [56]. Insulin binds to the α-subunit of its receptor and initiates β-subunit autophosphorylation, IRS-1 docking and increased PI3K activity. Activation of Akt and AS160 are required for GLUT-4 translocation but the distal or final steps have yet to be identified.

In healthy skeletal muscle insulin receptor and IRS-1 phosphorylation [57,58] as well as PI3K activity [57–60] are either unchanged or decreased immediately following exercise. Muscle contraction initiates a distinct set of cellular signaling cascades related to calcium flux (CaMKII), ATP turnover (AMPK) and physiological stress (p38 MAPK). These cascades have been shown to independently increase glucose transport and they can be differentially activated by the intensity of exercise [61]. Therefore, glucose disposal is regulated by nutrient- and contraction-mediated cellular events and emphasize the importance of exercise as a stimulator of glucose transport.

Exercise training is associated with a positive relationship between insulin-stimulated glucose disposal and PI3K activity in healthy skeletal muscle [34,62]. However, acute exercise [63] and short-term training [64] increase insulin-mediated glucose disposal in Type 2 diabetic muscle, independent of PI3K activity. The most important role of exercise in the treatment of Type 2 diabetest may be the regulation of gene and protein expression in skeletal muscle as GLUT-4 protein content, as well as other metabolic regulators, increase following exercise [3,64,65].

The contraction-mediated signaling cascades not only stimulate GLUT-4 translocation but also regulate metabolic gene expression and mitochondrial biogenesis [66,67]. Exercise training also leads to mitochondrial biogenesis including an increase in the number and size of mitochondria, increased Krebs cycle, β-oxidation and oxidative phosphorylation enzyme activity and increased uncoupling proteins and antioxidant production [68–71]. In conjunction with increased myoglobin and hexokinase activity, decreased phosphofructokinase and lactate dehydrogenase activity [68], cellular substrate utilization shifts toward lipid oxidation at rest and during submaximal exercise with decreased lactate production [72]. These data support the contention by Booth et al. that the maintenance of normal metabolic function requires skeletal muscle contraction mediated gene expression [3].

The increased oxidative capacity of the muscle cell following exercise training could partly explain the improved insulin sensitivity in...
subjects with Type 2 diabetes [73], despite a failure to improve insulin-stimulated intracellular signaling. Intramyocellular lipid (IMCL) is an important substrate during exercise and its proximity to the skeletal muscle mitochondria makes it an ideal source of energy. Interestingly, well-trained athletes, as well as obese and Type 2 diabetic subjects, have increased IMCL content [74]. The structural characteristics and distribution are similar, which make it unlikely that the quantity of IMCL is responsible for insulin resistance [75]. The mechanism responsible has yet to be determined but it has been speculated that the turnover in IMCL content associated with each exercise session, may be an important factor [76]. The reduced mitochondrial function associated with inactivity is reversible [77,78]. A lifestyle modification involving weight loss and increased exercise training in patients with Type 2 diabetes led to an increase in both mitochondrial content and functional capacity as well as improvements in insulin sensitivity [77]. It is not yet clearly understood how exercise increases mitochondrial biogenesis but recently epigenetic modifications and miRNAs have been shown to be important regulators of gene expression. It remains to be determined if exercise, or inactivity, play a role in the regulation of these processes.

The emerging benefits of exercise to patients with Type 2 diabetes

Exercise & the liver

The impact of aerobic exercise on hepatic glucose production has been well described [34,79]. These studies demonstrate that, for the same circulating insulin concentration during a hyperinsulinemic–euglycemic clamp, endogenous glucose production rates are lower in exercise-trained subjects. The reduction in hepatic glucose production has been attributed to enhanced insulin suppression of glycogenolysis and gluconeogenesis. Ropelle et al. recently performed an insulin tolerance test 8 hours after prolonged aerobic exercise in diet-induced obese rats [80]. They found improved insulin signaling associated with increased liver glycogen, and insulin-stimulated phosphorylation of Akt/protein kinase B and its downstream target FOXO1. In addition, the protein content of gluconeogenic enzymes and the interaction of the metabolic gene coactivator PGC-1α with FOXO1, which is associated with gluconeogenesis, were reduced. Collectively, these results suggest that the liver plays a direct role in the metabolic improvements attributed to aerobic exercise and provide a mechanism for the suppression of endogenous glucose production following exercise.

Another recent study by Hoene et al., provides evidence that the hepatic response is similar but much more rapid that skeletal muscle [81]. They found that a 60 min session of aerobic exercise rapidly induces the mRNA of gluconeogenic enzymes and genes associated with lipid oxidation including PDK4 and PPARGC1. This was accompanied by an increase in AMPK phosphorylation and IRS-2 protein content. Following glucose stimulation the tyrosine phosphorylation of IRS-1 and Akt were greater in the exercised animals. The reported increase in gluconeogenic enzyme mRNA reported in this study appears to contradict the findings of Ropelle et al. but the timing and stimuli are very different [80]. The immediate response to exercise is often characterized by a gene expression signature reflective of the physiological stress. During exercise the stimulus is for increased glucose production to maintain plasma glucose, but the adaptation to exercise improves insulin signaling and metabolic flexibility and facilitates a more efficient processing of substrate.

The enhanced metabolic functioning following exercise may also be related to changes in intrahepatic lipid content or turnover. In a cross-sectional study of 138 overweight and obese subjects Haufe et al. recently reported that aerobic fitness was positively correlated with insulin sensitivity but inversely related to intrahepatic, visceral and total lipid content [82]. The relationship between fitness and insulin sensitivity was maintained after adjusting for visceral and total fat but was no longer evident following adjustment for intrahepatic lipid. These authors suggest that the positive link between fitness and insulin sensitivity is mediated by hepatic lipid content. There is evidence to support a modest reduction of intrahepatic lipid content following exercise training in Type 2 diabetic patients, although there is a need for randomized controlled trials to provide definitive evidence [83].

We have also shown that insulin sensitivity can be increased following short-term exercise training in the absence of increased aerobic fitness or altered body composition [64]. These findings raise a question about the emphasis placed on total and visceral adiposity in the context of adaptations to exercise training, and suggest that a change in intrahepatic lipid may, in fact, be more relevant. Ideally, a decrease in total and
visceral adiposity is desired but a reduction in intrahepatic lipid may confer the same metabolic benefits. If this were the case it may be more advantageous to design an exercise prescription that would optimize the metabolic response in the liver and not necessarily focus on reducing total or visceral adiposity. There is increasing evidence for a direct impact of exercise on hepatic metabolic regulation but further investigations are required. A growing body of literature also supports the role of tissue–tissue cross-talk and communication. Hennige et al. have shown that enforced activation of protein kinase C signaling in skeletal muscle causes fatty liver, physical inactivity and brain insulin resistance. Therefore, the primary and secondary causes of metabolic dysfunction are poorly understood but this exciting area of research is likely to reveal a much more comprehensive interaction between tissues.

Exercise & the brain
There is a growing body of evidence to support the role of physical activity in the prevention and management of cognitive impairment. Given the increased prevalence of Alzheimer’s disease and dementia in Type 2 diabetes, there is a need for randomized controlled trials to investigate the impact of physical activity on cognitive function in these patients. In elderly men and women without cognitive impairment, a greater baseline level of physical activity or physical fitness is associated with a lower incidence of cognitive dysfunction. Barnes et al. found that a higher baseline aerobic fitness was associated with preservation of global cognitive function, attention, verbal memory and fluency in healthy older adults. Ettgen et al. followed 3903 participants without cognitive impairment at baseline for 2 years. At follow-up 207 (5.9%) of participants had developed incident cognitive impairment. They report a lower odds ratio for those who exercised one to two times per week (0.57, p = 0.01) and ≥3 times per week (0.54, p = 0.005).

Physical activity has also been associated with a reduction in incident dementia and the relative risk of Alzheimer’s disease. Podewils et al. found 480 incident cases of dementia in 3375 men and women, free from dementia at baseline, following a 5.4 year follow-up. Participants involved in ≥4 physical activities per week had a relative risk of 0.51 compared with those who engaged in ≤1 activity per week. Larson et al. found the incident rate of dementia was 19.7 per 1000 person years for those who exercise less than three times per week compared with 13.0 per 1000 person years for those exercising ≥3 times per week. Lautenschlager et al. found a modest improvement in cognitive function after conducting a randomized trial to investigate the effect of 6-month aerobic exercise intervention on cognitive function in subjects with memory problems.

The mechanism of exercise-mediated maintenance or enhancement of cognitive function is difficult to investigate but should form an important part of exercise research in the coming decade. Aerobic fitness is associated with reduced brain atrophy and preserved medial temporal lobe volume in patients with Alzheimer’s disease. Colcombe et al. reported an increase in gray matter volume in the frontal and temporal cortex as well as anterior white matter in older adults who had been randomly assigned to an aerobic exercise intervention compared with a stretching control group. It has also been proposed that exercise may preserve neuronal plasticity and increase synapses and dendritic receptors following injury. Other potential benefits of exercise include an increase in cerebral blood flow and influences on endocrine and immune responses.

These changes have been investigated in animal models and a number of neurotrophic, growth and signaling molecules have been identified. The expression and function of BDNF has been linked with behavioral improvements while IGF-1 and VEGF have been linked with angiogenesis and neurogenesis. In the context of diabetes it is also noteworthy that exercise improves insulin action in the brain. Flores et al. found increased insulin and leptin sensitivity in the hypothalamus of male wistar rats following acute exercise. These changes were associated with reduced food intake and provide a possible mechanism for exercise-mediated appetite suppression.

Exercise prescription
In spite of the evidence supporting a positive role for exercise in the treatment of Type 2 diabetes, there is still uncertainty regarding the optimal exercise prescription. It has been difficult to convince policy makers to fund exercise prescription programs to treat Type 2 diabetes, as they do with dietary or medical interventions, despite the known clinical and socioeconomic benefits.
There are many reasons why this may be the case and it is important that the key issues are debated. The evidence base for developing exercise programs has been strengthened by recently published randomized controlled trials [41–43]. This information should be used to lobby and advocate for diabetes-specific exercise programs. A second issue is that exercise and physical activity specialists often blame others for the lack of specific programs but fail to address the differences in opinion and approach of those implementing exercise research studies and programs. One approach has been to identify the lowest amount of exercise that elicits a positive clinical response, while the other has been to devise an exercise prescription for optimal therapeutic responses. These divergent approaches have led to large variations in study design, exercise intensity and frequency as well as research outcomes. It is reasonable to advocate for either of these approaches so long as the outcomes are quantified and appropriately translated into recommendations. The reality is that no one set of recommendations will be suitable for all patients with Type 2 diabetes. A debate on these issues is warranted and a number of issues should be considered.

In the first instance it is important to clearly define the purpose of the exercise program. This is dependent on a number of factors including glycemic control, the presence of complications, the duration of diabetes and the age of the patient. In otherwise healthy patients the primary goal of an exercise program, for patients with Type 2 diabetes, should be to improve insulin sensitivity and glycemic control. A secondary goal for these subjects could be to reduce body fat mass, which is also beneficial to insulin sensitivity. Glycemic control has been linked with exercise capacity in a cross-sectional study [100] and exercise training has been shown to reduce HbA1c in subjects treated with oral medications and those who are long standing insulin treated [46,101]. However, most studies report on a patient cohort with an average HbA1c between 7 and 8% [41–44]. The DARE [44] and HART-D [42] studies provide a good example as the former found that aerobic, resistance and combined training improved glycemic control while the HART-D found that only combined exercise lowered HbA1c. A subgroup analysis of the HART-D subjects found that aerobic training significantly lowered HbA1c in those who had an initial value greater than 7%. Therefore, it is arguable that exercise recommendations should also consider the baseline glycemic control.

However, it is possible that other factors such as the exercise stimulus, the duration of diabetes, gender and ethnic balance, and the management of medications could also influence the outcomes. The added difficulty in studying poorly controlled subjects with Type 2 diabetes is that they are more likely to have exercise-limiting complications. Therefore, the exercise prescription has to be modified, usually by decreasing the exercise intensity or limiting the type of exercise. These changes are necessary to ensure that secondary complications associated with high intensity exercise do not further the damage caused by retinopathy or peripheral neuropathy. As exercise, especially resistance training, increases systolic blood pressure it is possible that small vessels may hemorrhage during such activities. This does not mean exercise is ineffective in these populations but the magnitude of the response will be reduced.

The current exercise recommendations do not cater for the variety of factors that impact on a patient with diabetes. The most recent American Diabetes Association and American College of Sports Medicine guidelines recommend that individuals with Type 2 diabetes engage in at least 150 min of moderate intensity (40–60% of VO₂max) aerobic activity per week and suggest that additional benefits may be obtained from more vigorous intensity aerobic activity (>60% of VO₂max) [102]. In the absence of contraindications, resistance training at least twice but ideally three times per week should also be performed. The resistance training sessions should consist of at least five to ten exercises targeting all of the major muscle groups. A minimum of one set, but as many as three to four sets of ten to 15 repetitions to near fatigue should be performed. Over time the resistance should be increased so that only eight to ten repetitions can be performed. A combination of aerobic and resistance training three times per week may be of greater benefit to individuals with Type 2 diabetes than either type of training alone in terms of blood glucose control [42]. As the benefits of an acute exercise session on insulin sensitivity are relatively short, it is recommended that exercise sessions should not be separated by more than two consecutive rest days. These guidelines are very similar to those for the general healthy population and, as minimal recommendations, do not address the specific issues related to diabetes. Praet and van Loon have made a significant contribution...
to exercise prescription guidelines with their review article [103]. They offer guidelines and recommendations for patients based on the duration of diabetes, the initial fitness level of the patient, their BMI and the length of time they have been training. In addition, they integrate aerobic, resistance and interval exercise recommendations. This template is more comprehensive and should form the basis for developing a detailed exercise prescription.

The vast majority of research studies investigating the effect of exercise on patients with Type 2 diabetes are not designed to optimize exercise recommendations. This is acknowledged by the authors of meta-analyses who highlight the diverse range of exercise frequency, intensity and duration in published articles [33,45]. A recent review of the impact of training modalities on clinical outcomes found that there were no studies investigating the impact of:

- Training session volume/duration;
- Training frequency;
- High intensity interval exercise in patients with Type 2 diabetes [104].

Therefore, many of the guiding principles for exercise prescription are derived as secondary outcomes from research studies. A good example of this is the recommendation that exercise be conducted on nonconsecutive days. This recommendation is based on the impact of an acute exercise session on insulin sensitivity. Unlike other treatment modalities, exercise can improve insulin sensitivity after a single session [46,49,63]. This effect is transient and lasts for 12–40 h following exercise [54,105]. While this has raised very interesting mechanistic questions it also suggests that patients with Type 2 diabetes should exercise at least every second day to maintain and continue to improve insulin sensitivity.

An important challenge in devising an exercise prescription for patients with Type 2 diabetes is assessing cardiovascular risk. In most cases patients with Type 2 diabetes are recommended to have a stress test prior to commencing an exercise program. While it is important to minimize risk to the patient this guideline is not practical and potentially limits the therapeutic use of exercise. In the absence of a stress test clinicians are likely to adopt a more cautious approach and not an optimal exercise prescription for patients. It is important that a screening tool and/or exercise test be developed to assess and monitor patients with Type 2 diabetes in nonclinical settings. This could possibly include a submaximal exercise test with an upper threshold for diastolic and systolic blood pressure. It should also be possible to create an algorithm to predict risk during an exercise test based on heart rate, breathing rate, diabetes duration, glycemic control, and history of cardiovascular disease.

The current exercise recommendations for patients with Type 2 diabetes have been derived from research focused on determining the minimal intensity and duration of exercise to improve glycemic control. However, it appears that the minimal recommendations may not be sufficient to prevent weight gain. As most patients with Type 2 diabetes are overweight or obese, evidence suggests that they may gain weight over time even by adhering to the guidelines. The International Association for the Study of Obesity [106] and the Institute of Medicine [107,108] have concluded that a daily energy expenditure equivalent to approximately 500 kcal is necessary to prevent weight gain. The current recommendations would achieve approximately half of this target and suggest that total daily energy expenditure rather than the intensity and duration of a single-exercise session may achieve the best results. The recent evidence suggesting that physical inactivity may be a better determinant of disease risk would also support this view and further research in this area may significantly change our current views on the role of exercise prescription in the management of Type 2 diabetes [109].

The emphasis on exercise recommendations is being challenged by emerging evidence of a link between sedentary behaviors and health reviewed in reference [110]. The amount of sedentary time is reported to be at least 7.7 h per day or 55% of the measured time from the 2003 to 2004 National Health and Nutrition Examination Survey (NHANES) study [111]. Sedentary time, as determined by accelerometry or self-reported television viewing, is associated with increased fasting insulin [112], decreased glucose tolerance [113], markers of insulin resistance and the metabolic syndrome [114–117]. Recent evidence has shown that a decrease in muscle mass results from the activation of an atrophic signalling cascade and is not merely a reversal of the hypertrophic adaptation to training. Similarly, it is possible that sedentary time promotes cellular and biochemical changes that have a negative
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impact on physiological processes and ultimately health. However, it remains to be determined if these associations are independent of physical activity. It is possible that the current recommendations do not provide a sufficient stimulus to overcome the much greater sedentary time and that a greater emphasis needs to be placed on decreasing sedentary time as a strategy to enhance health.

Another argument to reduce the emphasis on exercise prescription is the issue of adherence. It has been reported that long-term adherence to exercise programs can vary from 10 to 80% [117]. A variety of factors may be responsible including time, motivation, readiness to change or adequate support structures. Large-scale exercise studies are very expensive to implement and require a high degree of supervision. The variance in findings from exercise training studies is partly related to the experimental design and verification of exercise adherence [33,45]. The greatest physiological benefits are often reported in studies where exercise sessions are supervised and monitored [33,45]. However, ‘real life’ application of exercise will require a novel approach and use a combined approach with decreasing physical inactivity. Given the greater benefits resulting from short term, supervised, exercise programs and the sustained benefits reported from lifestyle interventions [43], a periodically structured program (e.g., 3 months per year) may be sufficient to improve glycemic control if daily physical activity is increased. Alternatively, exercise referral programs that have a high degree of variety, social integration and enjoyment could be partly used to meet daily recommendations. The next big step may involve a joining of the two approaches where decreasing sedentary time is supplemented by exercise training sessions to achieve the overall goal of maintaining and improving health.

Conclusion
There have been significant advances in our understanding of the contribution of exercise to the prevention and treatment of Type 2 diabetes but significant challenges remain. In the pathophysiology of Type 2 diabetes, future research should focus on understanding the interaction between the CNS and peripheral metabolism. It will also be important to better understand the exercise training adaptation in noncontracting tissues such as the liver and brain and how miRNA and epigenetic modifications are influenced by acute and chronic exercise. In a practical and applied setting future research should focus on inactivity physiology and determine if a combination of decreasing sedentary time in conjunction with a prescribed exercise program would produce better adherence and clinical outcomes. Alternatively, daily energy expenditure targets could be used but this will require the development of monitors with greater accuracy and reliability. Specifically addressing exercise prescription there is a need for more studies to determine the impact of exercise mode and intensity on glycemic control. Finally, the future rests in researchers working together to provide novel and varied ways of increasing daily physical activity.

Future perspective
The next decade holds potential for exercise and physical activity research. In practical and applied research the focus is likely to shift from identifying minimal exercise recommendations that confer health-related benefits toward a decrease in sedentary time. The investigation of inactivity physiology will provide an alternative perspective on metabolic regulation and should complement behavior research designed to increase physical activity compliance. The role of prescribed exercise, while still playing an important role in diabetes treatment, will become a more valuable model of disease pathophysiology. In addition to contraction-mediated glucose transport and gene expression, the metabolic regulation of noncontracting tissues such as the liver and brain, following exercise, will provide valuable information on the development and progression of diabetes. It will also be necessary to determine if these changes are direct or secondary effects owing to tissue secreted proteins (e.g., myokines, adipokines). This research on tissue–tissue communication will also identify biomarkers that are responsive to exercise and could be used to predict the onset and progression of diabetes.

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