Exercise Strategies to Optimize Glycemic Control in Type 2 Diabetes: A Continuing Glucose Monitoring Perspective

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IN BRIEF The introduction of continuous glucose monitoring (CGM) several years ago enabled researchers to investigate the impact of exercise strategies on 24-hour glycemic control. Such unique information on the glucoregulatory properties of exercise will ultimately lead to more effective exercise programs to prevent and treat type 2 diabetes. This article reviews the role of exercise and physical activity in the treatment of type 2 diabetes, complemented by recent data obtained by CGM.

Although exercise is an important treatment strategy to improve long-term glycemic control in people with type 2 diabetes, the impact of exercise on 24-hour glycemic control has remained largely unexplored. The introduction of continuous glucose monitoring (CGM) several years ago enabled researchers to investigate the impact of exercise strategies on 24-hour glycemic control. Such unique information on the glucoregulatory properties of exercise will ultimately lead to more effective exercise intervention programs to prevent and treat type 2 diabetes. This article reviews the role of exercise and physical activity in the treatment of type 2 diabetes, complemented by recent data obtained by CGM. Based on current evidence, practical implications for the prescription of exercise in the treatment of type 2 diabetes are discussed.

Assessing Glycemic Control: Lessons Learned From CGM

The quality of glycemic control is generally assessed on the basis of patients' A1C values (1). This key therapeutic value reflects average blood glucose concentrations experienced during the preceding 2–3 months (2) and can therefore be considered as a measure of long-term glycemic control. The importance of A1C as a measure of long-term glycemic control is illustrated by its strong relationship with diabetes complications (3). For this reason, it is not surprising that blood glucose management is generally focused on lowering A1C values.

Nevertheless, because A1C reflects average blood glucose concentrations over a prolonged period of time, it does not provide much information on the prevalence and amplitude of hyperglycemic blood glucose excursions experienced throughout the day. Such information is highly relevant because acute hyperglycemic episodes have been associated with the development of diabetes complications independent from patients' fasting blood glucose or A1C levels (4–12). In addition, the level of glycemic variability, which reflects the frequency and amplitude of upward and downward blood glucose excursions throughout the day, has recently been implicated in the development of diabetes complications (13–15). Although glycemic control is often well characterized according to patients' A1C values, detailed

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insight into blood glucose excursions throughout the day is limited.

The introduction of noninvasive, ambulatory CGM devices ~15 years ago enabled the assessment of blood glucose concentrations throughout the day. Initial studies applying the CGM technique indicated that patients with type 2 diabetes with clinically acceptable A1C values may still experience excessive blood glucose excursions (16–18). In accordance, we found that patients with type 2 diabetes spend a large part of the day with blood glucose concentrations well above the acceptable upper limit (180 mg/dL) as defined by the American Diabetes Association and the European Association for the Study of Diabetes (19) (Figure 1). Such excess hyperglycemia was even observed in type 2 diabetic patients with an A1C level well below the treatment target of 7%. In fact, patients with an A1C <7% experienced hyperglycemia for as much as 24 ± 5% of the time.

These findings indicate that A1C values in the acceptable range do not guarantee blood glucose concentrations in the acceptable range. Therefore, treatment strategies should focus not only on lowering A1C levels, but also, more specifically, on controlling postprandial blood glucose excursions. Moreover, because postprandial hyperglycemia substantially contributes to the glycation of hemoglobin (i.e., A1C) (20,21), reducing postprandial hyperglycemia also promotes the achievement of desirable A1C levels (22).

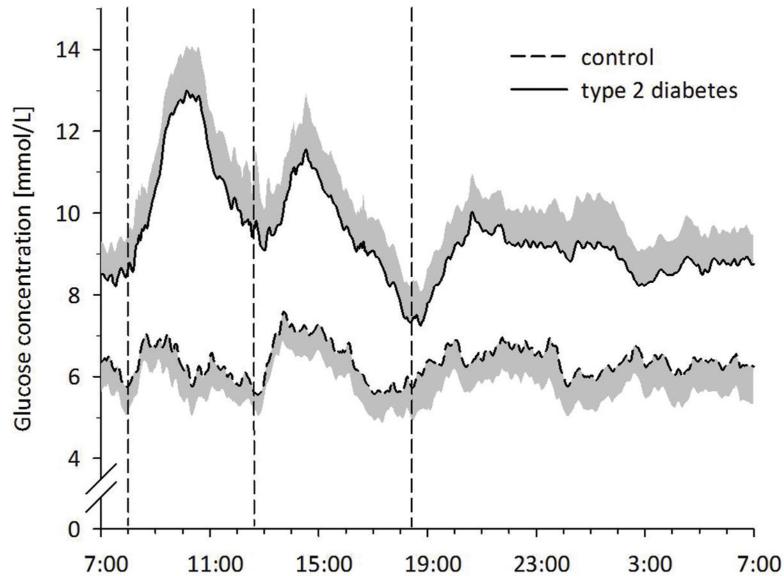

FIGURE 1. Average glucose concentrations over time in people with type 2 diabetes (n = 60; average 24-hour glucose concentration 171 ± 5 mg/dL) and healthy, normoglycemic, control subjects (n = 24; average 24-hour glucose concentration 113 ± 4 mg/dL) under standardized dietary, but otherwise free-living, conditions. The upper and lower margins of the 95% CI are indicated by the grey areas. Consumption of the main meals is indicated by the vertical dashed lines. Reprinted with permission from Ref. 19.

CGM to Assess Exercise-Induced Changes in Glycemic Control

The effect of structured exercise training on long-term glycemic control (i.e., A1C) has been extensively investigated. Recent meta-analyses indicate that the average reduction in A1C after long-term endurance or resistance exercise training can be as much as 0.5–0.8% (23–26). The benefits of exercise for glycemic control are largely explained by an increase in whole-body insulin sensitivity. It should be noted, however, that the effect of exercise training on insulin sensitivity is lost 5–10 days after cessation of exercise training (27–31). Therefore, it seems that the long-term effects of regular exercise on glycemic control (e.g., A1C) are attributed to the cumulative effect of transient improvements in insulin sensitivity and glycemic control after each successive bout of exercise, rather than to structural adaptations in insulin sensitivity (30,32,33). This is the reason why patients with type 2 diabetes need to exercise on a regular basis to achieve a sustained beneficial effect on blood glucose homeostasis. Moreover, this concept also emphasizes that the glucoregulatory properties of each individual exercise session are of key importance to achieving proper long-term glycemic control.

Before the introduction of the CGM technique, the acute and short-term effects of exercise could only be monitored in a laboratory setting by means of frequent blood sampling. Although interesting, laboratory-based experiments do not provide an answer to the question of whether exercise reduces blood glucose excursions in a real-life setting. For this reason, researchers started using blinded CGM to investigate the impact of acute exercise on 24-hour glycemic control under free-living conditions.

Recently, we investigated the impact of a single bout of moderate-intensity endurance exercise on 24-hour glycemic control in a large group of type 2 diabetic patients treated either with oral blood glucose–lowering medication or exogenous insulin (34). The exercise session was shown to reduce average glucose concentrations by ~16 mg/dL over the 24-hour period after exercise, along with a 30% reduction in the time spent in hyperglycemia (blood glucose >180 mg/dL). Exercise also lowered glycemic variability throughout the day, indicating a decline in the frequency and/or amplitude of glucose fluctuations. These results obtained by CGM clearly show the benefits of exercise for 24-hour blood glucose homeostasis.

Given the unique information on daily blood glucose homeostasis provided by CGM, this method has become increasingly popular as a means to investigate the impact of exercise strategies on 24-hour glycemic control in patients with type 2 diabetes. Interestingly, a study by Mikus et al. (35) showed that short-term (7 consecutive days) exercise training improves 24-hour glycemic control under free-living conditions, whereas the same intervention did not significantly lower patients' plasma glucose response to an oral glucose tolerance test (35). In addition, a recent meta-analysis of CGM studies indicated that exercise reduces postprandial blood glucose concentrations, whereas no effect was seen on fasting blood glucose concentrations (36). These findings support the view that the application of CGM under free-living conditions represents a more appropriate method to assess the impact of various treatment strategies on glycemic control than the standard laboratory-based blood glucose measurements. Another advantage of the CGM technique is that the intervention or monitoring periods can be kept relatively short. This allows for crossover intervention studies with the possibility to standardize or control for patients' medication, diet, and physical activity patterns. Consequently, the impact of exercise on glycemic control can be assessed without interference caused by long-term or acute changes in medication, diet, and habitual physical activity. It is important to note that the test-retest reliability of CGM has proven to be high under such standardized conditions (37).

In the past few years, the use of CGM in life sciences research has provided incremental knowledge on the effects of various exercise strategies on glycemic control. In the following sections, we will elaborate on the glucoregulatory properties of the main exercise characteristics, with special attention to the novel information provided by CGM.

What Type of Exercise Is More Effective in Improving Glycemic Control?

One of the main questions regarding exercise programs for patients with type 2 diabetes concerns the type of exercise that should be performed to optimize glycemic control. From a traditional perspective, the focus of exercise guidelines for type 2 diabetes has mainly been on the application of endurance exercise as the preferred exercise mode. This is likely attributed to the fact that most early exercise intervention studies applied endurance exercise (i.e., aerobic exercise) as a tool to improve insulin sensitivity and glucose tolerance.

In the past decade, however, resistance exercise (i.e., weight lifting) also has been associated with improvements in insulin sensitivity and glucose tolerance (38–41). Results obtained in large exercise intervention studies (42,43) and recent meta-analyses (24,26) indicate that the impact of resistance exercise on long-term glycemic control (i.e., A1C) is comparable to the impact of endurance exercise. Data obtained by CGM provides further support for the implementation of resistance exercise in exercise programs for patients with type 2 diabetes. Both resistance and endurance exercise were associated with a >30% decline in the prevalence of hyperglycemia over the 24-hour period after exercise (44). The benefits of both exercise modes for 24-hour glycemic control were observed not only in type 2 diabetic patients treated with oral glucose-lowering medication, but also in insulin-treated patients with type 2 diabetes. Even individuals with prediabetes (i.e., impaired glucose tolerance) experienced substantial improvements in 24-hour glycemic control after resistance and endurance exercise (44). This suggests that endurance exercise sessions can be exchanged for resistance exercise sessions and vice versa without compromising the benefits of regular exercise for glycemic control.

Practical Implications

Given the equal benefits of resistance and endurance exercise for long-term and 24-hour glycemic control, both exercise modes can be used in exercise programs to prevent or treat type 2 diabetes. This knowledge can be used to tailor exercise programs to individual patients' preferences and functional abilities. For example, resistance exercise might represent an attractive exercise mode for patients suffering from muscle weakness, cardiovascular complications, polyneuropathy, and reduced exercise tolerance, which generally reduce the feasibility of performing a strict endurance exercise regimen. Moreover, because type 2 diabetes is associated with an accelerated loss of skeletal muscle mass, strength, and functional capacity (45,46), it can be recommended to include at least two resistance exercise sessions per week in patients' exercise routine. For relatively healthy patients with no functional decline who are suffering from excess adiposity, endurance exercise likely remains the predominant type of exercise preferred to optimize fat loss. Resistance exercise is then required to help maintain fat-free mass while conforming to an energy-restrictive diet combined with endurance exercise training.

What Is the Impact of the Various Exercise Characteristics on Glycemic Control?

The efficacy of exercise to improve glycemic control largely can be attributed to the characteristics of the applied exercise program, including exercise intensity, exercise duration, and exercise frequency (33). The product of the main exercise characteristics (exercise duration × exercise intensity × exercise frequency) allows for an estimate of the exercise volume (or exercise dose), which can be regarded as the total amount of exercise performed within a certain period of time. The exercise volume can be expressed in different ways, such as the weekly amount of calories spent performing exercise, the metabolic equivalents accumulated over a week, or the total distance covered through walking, running, or cycling.

It is currently unclear whether the volume of endurance exercise ultimately drives the improvements in glycemic control, or whether the different characteristics of exercise (type, frequency, duration, and intensity) further modulate the impact of exercise on glycemic control.

Exercise Intensity Versus Exercise Duration

The intensity of an exercise routine is often viewed as a main determinant of subsequent improvements in glycemic control (33,47–49). Given the proposed relationship between the degree of glycogen depletion and subsequent improvements in insulin sensitivity (32,50), many exercise guidelines advocate endurance exercise at vigorous intensities to maximize endogenous glycogen use and increase the impact of exercise on glycemic control (47,49).

Although some studies have found superior benefits of high-intensity as opposed to moderate-intensity endurance-type exercise on insulin sensitivity (51,52), others have found that the volume of exercise training, rather than exercise intensity per se, is of prime importance with respect to the increase in insulin sensitivity (53,54). Studies that controlled for the volume of exercise (i.e., lower intensity compensated by a longer duration) found no surplus benefit of high-intensity as opposed to moderate-intensity exercise training for A1C levels (55,56).

Comparable findings were obtained by the use of CGM in patients with type 2 diabetes. Sixty minutes of low-intensity cycling (35% maximal workload) appeared to be at least as effective in reducing the prevalence of hyperglycemia throughout the day as a volume-matched bout of high-intensity cycling (30 minutes at 70% maximal workload) (57). This finding seems to agree with the comparable improvements in insulin sensitivity observed the day after performing low- to moderate-intensity as opposed to moderate- to high-intensity endurance exercise (58). Thus, most of the currently available evidence indicates that high-intensity exercise is not required to improve insulin sensitivity or glycemic control.

Exercise Frequency

The frequency at which exercise is being performed represents another important factor that may modulate the impact of exercise on glycemic control. Because the impact of each exercise bout on blood glucose homeostasis may last for up to 48–72 hours (59–61), exercise guidelines for type 2 diabetes generally state that exercise should be performed at least 3 days/week, with no more than two consecutive days between exercise bouts (47,49). However, it has been speculated that greater benefits for glycemic control could be achieved by performing exercise sessions more frequently. This view is supported by a recent meta-regression analysis showing that a higher frequency of exercise sessions is associated with greater benefits for glycemic control (62). This finding is not surprising because a higher frequency of exercise sessions is often accompanied by a greater total volume of exercise. It would be more relevant to assess whether greater benefits for glycemic control can be achieved by distributing the same exercise volume over more frequent exercise sessions.

By application of the CGM technique, it was shown that, for a fixed volume of exercise, short exercise sessions performed on a daily basis (30 minutes daily) offer no additional benefits for glycemic control compared to prolonged bouts of exercise performed less frequently (60 minutes every other day) (63). This finding implies that the total volume of exercise is more important than the frequency with which exercise sessions are being performed. In line with this view, a dose-response relationship has been observed between the volume of endurance exercise training and subsequent improvements in insulin sensitivity and glycemic control, irrespective of the frequency at which exercise sessions were being performed (53,64).

Practical Implications

Taken together, most of the currently available evidence indicates that the volume of exercise, rather than one of its components, is of key importance with regard to glycemic control. This concept has important implications for the prescription of exercise in the prevention and treatment of type 2 diabetes. When designing exercise programs, the initial focus should be on the selection of the appropriate volume of exercise. For example, we can prescribe patients to cover a distance of 18 km (~11 miles) per week. This volume can be covered either by running (high intensity) or walking (low to moderate intensity). Moreover, covering the distance either as three bouts of 6 km or as six bouts of 3 km likely induces the same benefits for glycemic control.

Although it sounds simple, selecting an appropriate exercise volume for individual patients will be challenging. Unrealistic targets can reduce patients' motivation, which may consequently affect their adherence to the exercise program (65,66). We should keep in mind that, although a large volume of exercise can induce greater effects than a small volume, a small volume of exercise is always better than no exercise at all.

After selecting the appropriate volume of exercise, the exercise characteristics (i.e., frequency, duration, intensity) can be used to tailor the exercise program to match individual patients' preferences and functional abilities. Patients with diabetes complications such as vascular complications or reduced exercise tolerance may not be capable of performing prolonged exercise sessions at higher exercise intensities. These patients may prefer to perform more frequent, shorter exercise sessions at a low or lower intensity. On the other hand, relatively healthy patients with a busy schedule may prefer to perform more intense exercise sessions, thereby allowing a short or shorter exercise duration to attain the predefined volume of exercise.

Exercise or Nonexercise Physical Activity to Improve Glycemic Control?

Despite the well-documented benefits of exercise in the prevention and treatment of type 2 diabetes, many patients with type 2 diabetes have difficulties engaging in or adhering to structured exercise intervention programs. The most cited reasons to abstain from regular exercise include lack of time, lack of motivation, lack of joy, physical discomfort during exercise, and resistance against exercise facilities (67). Therefore, it could be questioned whether engaging in a typical exercise intervention program is the most suitable physical activity intervention for all patients with type 2 diabetes.

It has been argued that physical activity strategies should focus more on increasing physical activity applicable to patients' daily life and home environment (68,69). In that respect, an increase in unstructured physical activities such as strolling, walking a dog, or performing light gardening or household tasks may represent a promising alternative to structured exercise. This view is supported by evidence from epidemiological studies, indicating that nonexercise physical activity is beneficially associated with glucose concentrations independent of moderate to vigorous intensity physical activity (70–72). Recent experimental studies have confirmed the benefits of nonexercise physical activity on postprandial blood glucose homeostasis. In this regard, repeated short bouts (2–15 minutes) of light physical activity during the postprandial phase have been shown to reduce postprandial glucose and/or insulin responses in nondiabetic individuals (73–76).

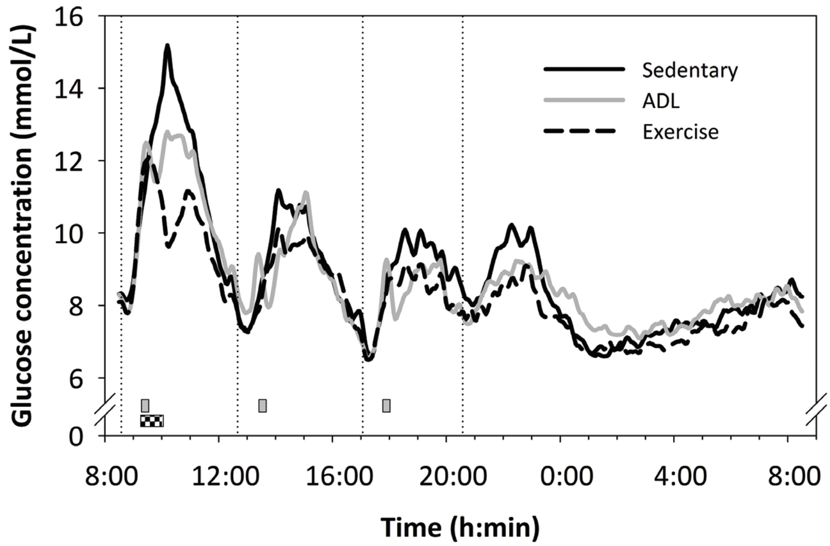

FIGURE 2. Twenty-four–hour glycemic profiles in type 2 diabetic patients under sedentary conditions and under conditions in which prolonged sedentary time was reduced by three 15-minute bouts of daily living activities (ADL; grey squares) or by a single 45-minute bout of moderate-intensity endurance-type exercise (checkered square). The dotted lines indicate the ingestion of the main meals (at 8:30, 12:30, and 17:00 hours) or snack (at 20:30 hours). The error bars are not shown for clarity. Reprinted with permission from Ref. 77.

Recently, we applied a comparable strategy in patients with type 2 diabetes (77). Glycemic control over 24 hours was assessed by CGM under sedentary control conditions and under conditions during which sedentary time was reduced by 15 minutes of strolling after each main meal (Figure 2). This study provided evidence that the introduction of repeated bouts of nonexercise physical activity (strolling) during the postprandial phase attenuates the postprandial rise in blood glucose and insulin concentrations in patients with type 2 diabetes.

Thus, besides structured exercise training, nonexercise physical activity can contribute to the prevention and treatment of type 2 diabetes. Although an increase in nonexercise physical activity could overcome many of the barriers associated with the implementation of structured exercise, future studies are needed to evaluate whether this strategy leads to higher adherence rates and comparable or better long-term clinical benefits when compared to the implementation of more structured exercise intervention programs.

Practical Implications

Recent evidence suggests that an increase in nonexercise physical activity is effective in reducing postprandial hyperglycemia and improving glycemic control. Therefore, patients with type 2 diabetes should be encouraged to undertake light physical activity frequently throughout the day. Even very short bouts (2–15 minutes) of light physical activity are associated with substantial improvements in glycemic control. This strategy seems to be most effective when these activities are implemented in the post-prandial state, thereby attenuating the postprandial rise in glucose concentrations (78). Because short bouts of light physical activity can be implemented easily in daily life, this strategy seems to be particularly valuable for patients who are unable or reluctant to participate in a more structured exercise program.

Conclusion

Although exercise is an important treatment strategy to improve long-term glycemic control in people with type 2 diabetes, the impact of exercise on 24-hour glycemic control has remained largely unexplored. The introduction of CGM several years ago enabled researchers to assess the impact of exercise strategies on 24-hour glycemic control. The use of this technology demonstrated that a single bout of exercise reduces the prevalence of hyperglycemia throughout the subsequent 24-hour period. In this regard, resistance and endurance exercise appear to be equally effective in improving 24-hour glycemic control.

Moreover, recent data from CGM studies suggest that the volume of exercise, also referred to as the exercise dose, is the main determinant of exercise-induced improvements in glycemic control. Thus, when designing exercise programs, the initial focus should be on the selection of an appropriate volume of exercise. After selecting an appropriate volume of exercise, the other exercise characteristics (i.e., frequency, duration, and intensity) can be used to tailor the exercise program to match patients' preferences and functional abilities.

In addition to structured exercise, nonexercise physical activities such as strolling, gardening, and performing household tasks have been associated with benefits for glycemic control. Therefore, health care professionals should encourage patients to undertake such activities frequently throughout the day.

Duality of Interest

No potential conflicts of interest relevant to this article were reported.

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