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Physical Activity and Type 1 Diabetes: Time for a Rewire?

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Abstract

While being physically active bestows many health benefits on individuals with type 1 diabetes, their overall blood glucose control is not enhanced without an effective balance of insulin dosing and food intake to maintain euglycemia before, during, and after exercise of all types. At present, a number of technological advances are already available to insulin users who desire to be physically active with optimal blood glucose control, although a number of limitations to those devices remain. In addition to continued improvements to existing technologies and introduction of new ones, finding ways to integrate all of the available data to optimize blood glucose control and performance during and following exercise will likely involve development of "smart" calculators, enhanced closed-loop systems that are able to use additional inputs and learn, and social aspects that allow devices to meet the needs of the users.

Keywords

exercise, technology, insulin, artificial pancreas, physical activity, type 1 diabetes

Physical activity (PA) for people of all ages living with type 1 diabetes (T1D) is associated with many well-established health benefits, including improved cardiovascular fitness, better bone-health and enhanced psychological well-being.[1,2] Despite these benefits, most adults with T1D participate less frequently in PA than their nondiabetic counterparts[3] and may adopt unhealthy lifestyles that contribute to cardiometabolic risk.[4] Although the reasons for this are multifactorial, including concerns over loss of control and low fitness levels, the overriding barrier to PA appears to be fear of severe hypoglycemia, coupled with a lack of knowledge of effective strategies for hypoglycemia avoidance.[3] Moreover, overall glycemic control (measured with glycated hemoglobin, or A1C, levels) with exercise has shown mixed results in T1D studies, with some demonstrating benefits[5-7] and others no improvement in A1C following aerobic or resistance training.[8,9] For overall glycemic control to be enhanced, individuals with T1D are required to skillfully balance insulin dosing and food intake to maintain blood glucose levels in a more normal range before, during, and after exercise.[10-13] Although many obstacles to safe and effective exercise participation remain, present and future technologies should assist more people with T1D to become and remain physically active to improve their health and reduce the negative impact of diabetes on participation in competitive sports and activities.[14,15]

What Complicates Diabetes Control During Exercise?

To optimize control of blood glucose levels during exercise, individuals must be aware of factors that can complicate glycemic management. Among these are participation in varying types of PA, differences in insulin regimens and food intake for exercise, and the necessity of maintaining normal or nearly normal blood glucose levels before, during, and after activities (Figure 1). Balancing all of these factors can be overwhelmingly challenging for many, who may choose instead to be less active to avoid hypoglycemia in particular.[3]

Exercise Variables

The impact of exercise on glucose homeostasis is influenced by the type, intensity, and duration of the activity. Participation in aerobic, sprint, and resistance training can result in widely varying blood glucose responses.[16,17] Differences in exercise intensity also impact outcomes, with high intensity activities causing a greater release of counterregulatory hormones like epinephrine and glucagon that can cause immediate and lasting elevations in blood glucose levels.[18,19] In fact, an all-out sprint as short as 10 seconds can have a lasting effect on glycemic balance.[18,20] Duration also has an impact, with

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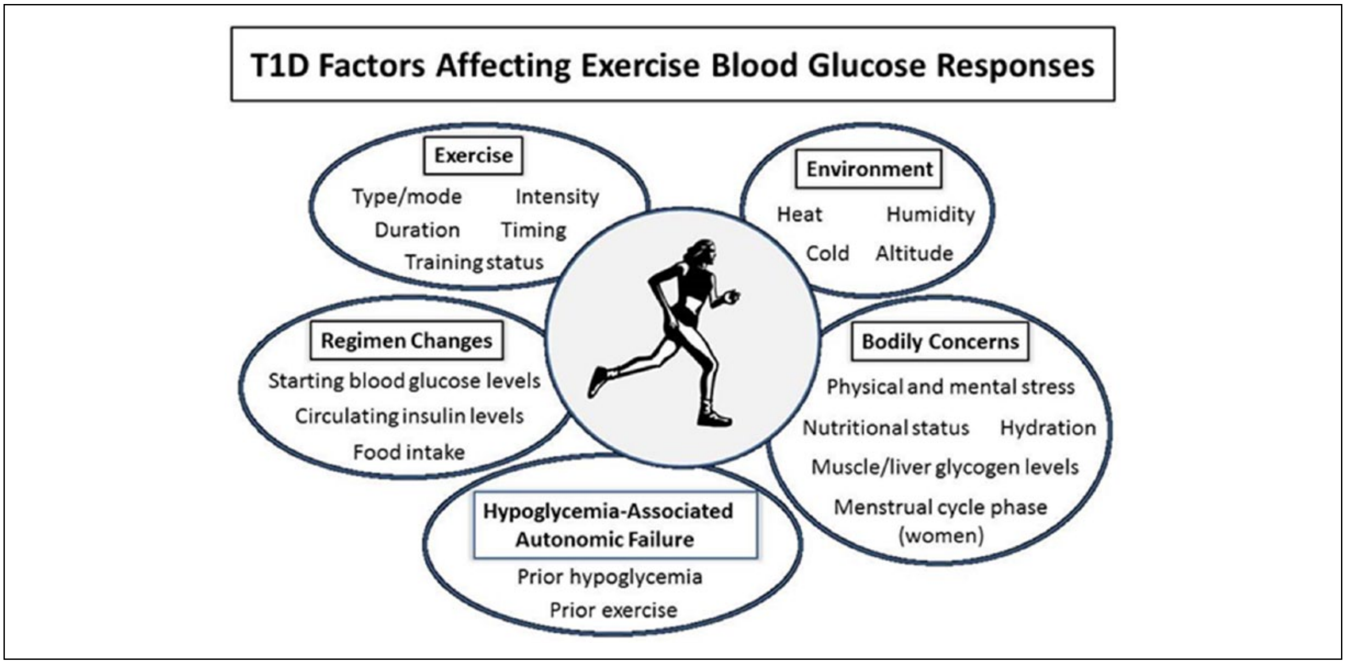

Figure 1. Type 1 diabetes factors affecting exercise blood glucose responses.

longer periods of exercise generally resulting in greater blood glucose use and the risk of hypoglycemia, although large individual variations in hormonal responses to prolonged exercise of varying types have been demonstrated in athletes with T1D.[21,22] Exercising more than once in a day or on more than 1 day in a row can also affect blood glucose outcomes during the exercise itself and afterward.[23] While highly trained individuals with T1D can achieve the same cardiopulmonary exercise responses as trained subjects without diabetes, their responses are reduced by poor glycemic control.[24] The impact of PA is also complicated by the nature of the sport where periods of intense activity are interspersed with periods of much less activity, for example, American football, soccer, and basketball.

Individuals with T1D are frequently unable to adequately alter endogenous insulin levels and experience normal hormonal glucose counterregulation during and following exercise. Consequently, they are at risk for early and late hypoglycemia and also hyperglycemia. The risk of overnight and next-day hypoglycemia is particularly problematic if moderate to vigorous exercise is undertaken in the afternoon or early evening.[25,26] Late-onset hypoglycemia following exercise increases with the duration of exercise and the fitness of the exercisers, and activities lasting 90 to 120 minutes double the risk of hypoglycemia in adolescents and young adults.[26]

Insulin Regimens

Glycemic control with PA is also complicated by the fact that different insulin regimens and delivery systems are available for T1D. Most insulin regimens are based on a basal-bolus approach.[27,28] Insulin pumps using a rapid-acting insulin analog are programmed to deliver small amounts of this insulin frequently in small doses to cover basal needs, with user programming of bolus amounts for meals, snacks, and corrections of glucose levels based on need.[29] In a small clinical study, adults with T1D using insulin pump therapy and performing regular moderate-to-heavy intensity aerobic exercise experienced less postexercise hyperglycemia compared with multiple daily injections (MDI) without increasing the risk of postexercise late-onset hypoglycemia.[30] However, even when using insulin pump therapies instead of MDI, individuals still can experience wide variability in glucose profiles before, during, and after exercise.[31]

Carbohydrate and Food Intake

Particularly when insulin adjustments are not made for PA (as is frequently the case for spontaneous activities) or the activity is prolonged in nature, balancing carbohydrate intake with needs based on the intensity and duration of PA and circulating insulin levels becomes critical for prevention of hypoglycemia.[32-34] Fuel utilization in T1D adults undertaking aerobic exercise during euglycemia is similar to that in healthy individuals, with a greater reliance on carbohydrate as the primary fuel for moderate to vigorous activity and a shift toward greater lipid oxidation during prolonged exercise. However, during hyperglycemic exercise, carbohydrate and blood glucose use are both increased without sparing muscle glycogen.[35] PA undertaken during injected insulin peaks increases reliance on carbohydrate intake to prevent hypoglycemia, but also does not reduce muscle glycogen use.[36] After exercise a mix of macronutrients may more efficiently prevent later-onset of hypoglycemia.[37,38] Adequate carbohydrate intake during and following exercise is, therefore, critical for effective PA participation and hypoglycemia prevention.

Optimal Glycemic Balance for Athletic Performance

Having a competitive advantage in athletic events requires prevention of both hypoglycemia and hyperglycemia during and following exercise is, therefore, critical. Particularly when individuals experience recurrent low blood glucose levels, they can develop hypoglycemia-associated autonomic failure[39,40] that has the potential to affect subsequent counterregulatory responses to PA.[23,41] As a corollary, antecedent physiologic increases in cortisol (equivalent to levels during hypoglycemia) have been shown to blunt neuroendocrine and autonomic nervous system responses during subsequent exercise in adults with T1D.[42] Inability to prevent hypoglycemia during training and competitive events will assuredly reduce exercise performance.[21,43]

What Does Current Technology Offer to Diabetes Management With Exercise?

A number of technologies are already available to support PA in people with T1D. Among these are devices that measure and track heart rate, intensity of movement, calories expended, distance traveled as well as diabetes-specific devices including insulin pumps, blood glucose monitoring systems, and continuous glucose monitors.

Wearable Tracking Devices and Performance Indicators

There is increasing interest in the use of wearable sensors that are able to measure physiological parameters including heart rate, distance traveled, and calorie expenditure.[44,45] Many utilize smartphone technologies (apps) that can communicate with a variety of fitness and health tracking platforms. For example, continuous data from ankle triaxial accelerometers can be transmitted from the home and community via Wi-Fi or a smartphone to a remote data analysis server and compile data and reports on walking speed, duration of exercise, and even the type, duration, and energy used during exercise.[46,47] Other devices can track food intake (entered by the user); calculate calories in and out; estimate carbohydrate intake (in grams); measure body weight, percentage body fat, and body mass index; estimate power (wattage) and transmit results wirelessly to online accounts; and display graphs, trends, daily, and weekly goals.[48]

For people with T1D accurate estimation of carbohydrate (higher glycemic index carbohydrates in particular) and calorie intake, balanced with energy expenditure during exercise, is critical for maintaining euglycemia.[49] The glycemic effects of protein and fat may also be relevant for PA.[50-52] With current devices, although it may be possible to estimate carbohydrate and other fuel use based on heart rate, characteristics of the activity (such as intensity and duration), calorie expenditure, and blood glucose responses, a considerable amount of variability is still likely to exist due to the potential impact of other factors like variations in subcutaneous insulin absorption and fluctuations in insulin sensitivity.[53-55]

Insulin Delivery and Pumps

Despite many advances in insulin pumps, syringes, and pens over the past several decades, the delivery of pumped or injected insulin remains hindered by its subcutaneous delivery and rates of absorption, which generally lags behind carbohydrate digestion and absorption and creates a mismatch between the postprandial rise in blood glucose and insulin availability. For metabolism to be normal, exogenous insulin would need to be delivered through the portal vein as occurs in nondiabetic individuals. The liver maintains glycemic balance at rest and during exercise by either releasing or storing glucose in response to changes in blood glucose levels; in people without diabetes, insulin released directly from the pancreas following food ingestion results in a dual trigger of elevated glucose and insulin postprandially that promotes glycogen storage. In individuals with T1D, the liver is less effective at both storing glucose as glycogen for later release and releasing adequate amounts of glucose in response to decreases in blood levels during exercise with elevated peripheral insulin levels, even though increased rates of hepatic glucose production apparently occur in T1D at both times through increased gluconeogenesis.[56,57]

One advance that insulin pumps offer over MDI regimens is that pumps allow users to change basal insulin delivery around the time of exercise to more closely replicate a normal physiological response, whereas users of basal insulin that is injected once or twice daily are less able to respond quickly enough to changes in insulin needs.[29,30] In 1 study, for adults with T1D performing 45 minutes of regular moderate-to-heavy intensity aerobic exercise, use of insulin pump therapy limited postexercise hyperglycemia compared with MDI and was not associated with increased risk for postexercise late-onset hypoglycemia. 30 Most pumps also now incorporate bolus calculators to take into account any remaining insulin from the last bolus, but the duration of insulin action used in such calculators has yet to be standardized to assist in making a more effective reduction of circulating insulin levels in the hour or 2 prior to exercise.[58] Using pumps leads to additional practical considerations based on the type of PA, though, such as what to do with the infusion set (if the pump is not disconnected[59]), whether the pump is waterproof, and how environmental factors may affect the insulin in the pump (if still connected or tubeless).

Home Glucose Monitors

The ability to test blood glucose levels before, during, and after PA is clearly important for managing glycemia and improving exercise performance, regardless of the athletic abilities of the exerciser.[60] Although the time required and size of the blood drop needed for an accurate measurement have decreased considerably over recent years, a lancing device is still required to obtain a glucose sample. The smallest self-monitoring blood glucose device is now smaller than the usual flash drive (and can fit into a port of an iPhone to display results), and most of these monitors are still standalone devices. Some of them are integrated with insulin pumps, but remain open-loop systems leaving decision making up to users and/or their health care teams.

Continuous Glucose Monitors

A second advance in home-based glucose monitoring is the development of continuous glucose monitors (CGM). In 1 study on runners with T1D, CGM use was found to be helpful in identifying asymptomatic hypoglycemia or hyperglycemia during and after a marathon.[61] In adolescents with T1D using CGM, participating in afternoon moderate-to-vigorous PA was found to increase the risk of overnight and next-day hypoglycemia.[26] At a summer sports camp, adolescents with T1D were able to use CGM coupled with a novel carbohydrate intake algorithm to prevent hypoglycemia and maintain euglycemia during exercise, particularly if they ingested carbohydrates in adequate amounts when trend arrows on the device alerted them of a drop in glycemia.[32]

Current CGM systems have their limitations, including changes in accuracy with duration of sensor wear, precision issues, and skin irritation and problems with sensor adhesiveness.[62-64] However, the marked inaccuracy and lag time of CGM readings when blood glucose levels change rapidly within the physiological range (such as during exercise) should be minimized for optimal CGM use in glycemic management.[64] Future CGM systems will benefit from further increasing their accuracy and reliability and ideally utilize algorithms that can adapt over time to individual differences in user physiology.[65,66] The most critical improvement in CGM systems that would increase their use (without breaks) by a larger proportion of individuals with T1D during exercise is the ability to measure *blood glucose* (not interstitial glucose) to give the user (or any integrated system) "real-time" values that are actually reflective of blood glucose at that exact point in time and not lagging behind when glucose levels are changing rapidly during exercise,[64] and such technologies are currently not available.

Other advances combining some of these devices are in the early stages. One promising approach includes the measurement of heart rate variability (HRV). Adolescents who engage in spontaneous moderate aerobic activity have improved autonomic regulation.[67] Moreover, in a very recent study, hypoglycemia detection accuracy and lead time were significantly improved by a novel algorithm involving both HRV and CGM data together.[68] This approach, as compared to the CGM device alone, has the potential to make the combination of such tools of immense potential value to individuals with T1D to detect hypoglycemia during and following PA, particularly if they experience hypoglycemia unawareness or autonomic failure. Hypoglycemia-associated autonomic failure following prior exercise or hypoglycemia is only experienced with peripheral insulin delivery in T1D.[23,41,57,69-75]

What Should Future Technology Offer to Best Manage Diabetes With Exercise?

An even bigger challenge than perfecting the devices themselves (and many of them have advanced substantially over several decades) is finding ways to integrate all of the available data to optimize blood glucose control and performance during and following exercise undertaken by individuals of all ages with T1D. Integration will likely involve "smart" calculators, better closed-loop systems that are able to do adapt and learn, and social aspects that allow devices to meet the needs of the users.

Calculators for Exercise

Currently, insulin bolus calculators are available on most insulin pumps that take into account the timing of prior insulin dosing, usual absorption rates, insulin sensitivity, and correction factors. These calculators are also being integrated into glucose meters and portable device applets for use with multiple daily injections.[76] However, none of these calculators currently account for the effects of PA beyond offering a percentage correction for exercise in the general sense (Roche device), and they may use inappropriately short estimates of duration of insulin action that can cause unrecognized "stacking" of insulin, leading to unexplained hypoglycemic events, particularly when exercise is an added variable.[58]

The primary goal of an ideal exercise calculator for T1D is prevention of both hypoglycemia and hyperglycemia during the activity and during the 24- to 48-hour period following exercise. Hypoglycemia most commonly develops during, in the immediate postexercise period, and then again around 7 to 11 hours later in a biphasic manner,[25] meaning that many individuals experience a secondary decline in their postactivity glucose levels during nighttime hours. Glycemic management with intensive insulin therapy should ideally be accomplished without inducing weight gain or increasing the number of hypoglycemic events, which frequently requires fine-tuning of both carbohydrate intake and insulin dosing.[49]

Prediction of glycemic responses for the purposes of a calculator may be further complicated by use of other medications with insulin like pramlintide.[77] Likewise, the presence of certain diabetes-related complications like gastroparesis, which is estimated to affect about 40% of those with T1D, can make the absorption of food erratic and delayed and glycemic responses less predictable.[78,79]

Therefore, to be truly effective, a calculator will benefit from being able to do most, if not all, of the following:

- Make general suggestions about insulin and food intake to allow for adjustments prior to the start of PA (such as lowering basal insulin prior to the activity and not just during and following it);[80]
- Make more specific recommendations for regimen changes based on user input or measured physiological data in real time related to the type, intensity, and duration of PA that is being undertaken by the individual;[17,81,82]
- Create updated recommendations when the plan for PA is altered during the activity, such as a change in duration, intensity, or type;[17,82]
- Factor in the impact of the individual's starting blood glucose level on subsequent responses to PA;[83]
- Predict hypoglycemia in advance or in real time based on specific user input about PA, prior insulin timing and dosage, and prior or planned food intake during activity and give recommendations for its prevention during and following activity;[84]
- Predict hyperglycemia and give recommendations for regimen changes to prevent or correct PA-induced increases in blood glucose;[83]
- Account for use of medications or the presence of diabetes complications that slow absorption of ingested carbohydrates taken for PA;[85]
- Factor in the potential confounding effects of prior hypoglycemia and exercise resulting in hypoglycemia-associated autonomic failure during subsequent exercise;[71,72] and
- Adapt to prior input to make even more "intelligent" recommendations for maintenance of glycemia during subsequent PA of a similar nature.

Artificial Pancreas Systems

This involves integration of CGM devices, insulin delivery via a pump, and an algorithm control system to manage blood glucose levels with minimal or without user input, thereby creating an external device-driven artificial pancreas (AP) system. Some investigators have suggested that dual hormone delivery (ie, both insulin and glucagon) may work more effectively in preventing hypoglycemia than insulin alone,[86-91] while others continue to work on developing a system using insulin delivery only.[92-98]

Researchers have begun to collect a variety of PA data from existing devices to assist them in creating functioning algorithms.[99-103] Early work by Turksoy et al,[103] Breton et al,[100] and Stenerson et al[104] suggest that early detection of PA is feasible using heart rate and/ or a multisensory device like the Bodymedia armband and that this information will enhanced closed-loop control and improve both the immediate hypoglycemia risk and the latent effect. Use of adaptive control and/or predictive design that will use additional PA inputs may be beneficial especially in the prevention of latent hypoglycemia. However, any closed-loop system that is developed using current CGM technologies and insulin delivery methods (subcutaneous) will be limited by slow insulin action and slow insulin clearance and lagging of glucose response in case of fast negative rate of change. This may affect AP systems that are based solely on glucose measurements.[64,105] PA variables that are introduced and/or exacerbated by activity include the rates of blood glucose and glycogen use during activity, effects of any residual insulin being absorbed into the bloodstream from a subcutaneous depot, and inability of the system to respond to rapid changes in blood glucose. For more information on the progress in the development of automated glucose control, readers are directed to other comprehensive review articles.[106-109]

Ideally any AP closed-loop system will be able to cope with PA with minimal or no user intervention. In a recent study, adolescents and adults with T1D involved in a closed-loop insulin delivery system participated in midafternoon exercise (brisk walking for 60 minutes, a moderate activity) and still exhibited a lower risk of nocturnal hypoglycemia following exercise and an increased percentage of time spent in their target blood glucose range.[110] Moreover, adding a heart rate signal to another closed-loop system further limited the risk for hypoglycemia during and immediately after exercise.[100] The challenge of the current AP systems that are based on subcutaneous delivery of insulin and glucose sensing is that the system is limited by the fact that even if PA is detected at the onset of the event, it may be too late to prevent the acute onset of hypoglycemia without user intervention or the use of glucagon. These results suggest that, while waiting for technology to advance to the point that a full closed-loop AP system would work optimally, simply perfecting a system that could provide closed-loop insulin delivery at night or help make better exercise adjustments may be of benefit to maintaining glycemic balance during and following PA participation.

Pattern Recognition and Learning

For an exercise calculator or a closed-loop AP system to work effectively, access to real-time data about physiological variables like heart rate, movement (with an accelerometer), and possibly other biometric data like blood lactate levels during more intense training, is likely a necessity.[111] Beyond just receiving these data, it would benefit from having the capacity to analyze and integrate these inputs into algorithms that would identify regimen changes in real time and be able to predict such a change prior to the start of the PA, enabling the system to take preventive actions to help to maintain glycemia and optimize performance outcomes.

For real-time learning to take place with a calculator or for any integrated (eg, closed-loop) system, it should be able to collect and analyze data in real time, use algorithms developed using mathematical modeling that can adapt to new input from users and associated devices, and decrease variability in outcomes over time with more relevant and individualized recommendations for diabetes regimen management.[65,66] Ideally, such systems or machines would also be able to quantify or integrate users' more subjective responses to them, thereby enhancing their perceived value.[112] For that to be the case, technologies will eventually have to advance to be even more accurate and adaptable than they currently are to integrate analyses from multiple sources, participants and types of PA, along with having adaptive machine learning to allow for personalization of advice.

Regulated and Unregulated Devices

To be effective in both preventing glycemic swings above and beyond target values and supporting the achievement of personal PA goals, technologies will benefit from being able to

- Be interoperative;
- Avoid barriers related to health literacy;
- Understand the potential value of physiological data affected by PA; and
- Provide specific decision support.

Providing specific decisions for an insulin-regulated person with T1D will require evidence of effectiveness and safety of any devices or integrated system. The journey along a regulatory pathway can be problematic and dissuade innovators from participating or focusing on the consumer electronic market in general. One option would be to consider approval of hybrid systems that incorporate regulated devices measuring specific variables like glucose levels and insulin pumps or other technologies that can predict the potential for hypoglycemia, but with a less burdensome approval pathway for PA devices that indirectly contribute to the development of decision support exercise. Of course, with the complexity of blood glucose responses to PA, any hybrid system would still have to be able to lower the risk of hypoglycemia compared to using those same devices with greater user input.

Social Integration

Systematic reviews of internet-delivered interventions for PA have shown modest effectiveness when self-monitoring, goal-setting, or feedback was included.[113,114] Recently, the use of social networking has demonstrated a modest benefit for health and weight management,[115-117] although at present there is a paucity of studies focusing on diabetes. One potential area of benefit involves the use of video games, which are especially popular with younger people.[118-120] A recent approach has been to create augmented reality games whereby participants combine real-world with virtual activities with PA embedded within the game (such as Wii Fit).[119,121,122] This type of approach may be especially beneficial for individuals of all ages who are geographically isolated or have lower levels of peer support.

Currently, many web sites and apps allow users to share their exercise goals and results with friends, family, and health care team, but these programs currently lack the ability to integrate all of the biometric and other collected data to be shared with others in real time to enhance the experience. In a recent review of mobile apps, the available ones for diabetes management support self-management tasks like physical exercise, insulin dosage or medication, blood glucose testing, and diet, but also include other support tasks decision support, notification and alerts, tagging of input data, and integration of social media.[123] Overall, app usage appears to improve attitudes toward diabetes self-management, but app use may be limited by lack of personalized feedback, issues with ease of data entry, and ineffective integration with patients and electronic health records.

In adults with T1D, the use of a diabetes-related smartphone application combined with weekly text-message support from a health care professional and usual care was able to significantly improve glycemic control.[124] Imagine the diabetic exerciser of the future who receives feedback from a friend or diabetes educator in real time who has access to his or her data and can share successes, failures, and learning that can improve the next exercise experience. In a world severely lacking in exercise motivation, such a system may be the answer to keeping everyone more active and healthy, not just individuals with T1D.

Conclusions

While technological advances have allowed exercisers with diabetes to progress toward more effectively managing their blood glucose levels during various types of physical activities, technology is still far from fully removing the fear of hypoglycemia that is the strongest impediment to undertaking regular exercise with T1D. The use of present and future technologies will likely assist more people dealing with T1D to become and remain physically, as well as perform optimally in competitive sports and activities. The future integration of various technologies will likely make exercise a much safer and more effective undertaking and result in a greater perceived value related to both health and glycemic management.

Abbreviations

A1C, glycated hemoglobin; AP, artificial pancreas; CGM, continuous glucose monitors; HRV, heart rate variability; MDI, multiple daily injections; PA, physical activity; T1D, type 1 diabetes.

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