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REVIEW

The Athlete with Type 1 Diabetes: Transition from Case Reports to General Therapy Recommendations

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Abstract: Fear of hypoglycemia is a common barrier to exercise and physical activity for individuals with type 1 diabetes. While some of the earliest studies in this area involved only one or two participants, the link between exercise, exogenous insulin, and hypoglycemia was already clear, with the only suggested management strategies being to decrease insulin dosage and/or consume carbohydrates before and after exercise. Over the past 50 years, a great deal of knowledge has been developed around the impact of different types and intensities of exercise on blood glucose levels in this population. Recent decades have also seen the development of technologies such as continuous glucose monitors, faster-acting insulins and commercially available insulin pumps to allow for the real-time observation of interstitial glucose levels, and more precise adjustments to insulin dosage before, during and after activity. As such, there are now evidence-based exercise and physical activity guidelines for individuals with type 1 diabetes. While the risk of hypoglycemia has not been completely eliminated, therapy recommendations have evolved considerably. This review discusses the evolution of the knowledge and the technology related to type 1 diabetes and exercise that have allowed this evolution to take place.

Keywords: exercise, physical activity, blood glucose, insulin, carbohydrate, continuous glucose monitoring

Introduction

Type 1 diabetes is a chronic health condition that involves the auto-immune destruction of pancreatic islet cells. This destruction results in insulin deficiency and a need for exogenous insulin. Onset of the disease typically occurs in childhood or early adulthood. As a result, individuals with type 1 diabetes develop health complications at younger ages than people without diabetes[1,2] or even those with type 2 diabetes.[3] Complications include cardiovascular disease (the leading cause of death among individuals with type 1 diabetes),[4] an increased risk of retinopathy,[5] nephropathy[6] and neuropathy,[6,7] along with accelerated bone[8] and muscle loss[9] with aging.

It is currently recognized that exercise and physical activity play an important role in self-care for the prevention and management of these diabetes-related complications. Recent cohort and cross-sectional studies involving individuals with type 1 diabetes have found an inverse correlation between diabetes-related complications and self-reported leisure time physical activity.[10–14] Increased physical activity frequency[10–12,14] and intensity[13] are associated with a lower incidence and prevalence of cardiovascular disease and cardiovascular disease risk factors.[14] They are also associated with a decreased frequency and severity of diabetes complications,[15–18] increased life expectancy[16–18] and improved quality of life[19,20] in this population. Unfortunately, if not properly managed

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physical activity and exercise can cause large and rapid declines in blood glucose, increasing the risk of hypoglycemia during exercise, and can also cause hyperglycemia post-exercise for several hours.[21] The introduction of this volatility in blood glucose levels may be one of the reasons that more than 60% of individuals with type 1 diabetes are physically inactive.[11,22] Furthermore, women with type 1 diabetes tend to report lower physical activity levels than men with the same condition.[11,23] Fear of hypoglycemia has been identified as one of the main barriers to exercise and physical activity in this population.[24]

With improvements in insulin formulations and diabetes technologies (insulin pumps, continuous glucose monitors, closed loop systems), blood glucose levels before, during and after exercise have become much easier to monitor. In addition, a plethora of exercise and physical activity-related studies over the past 50 years have greatly improved the level of knowledge around the impacts of different activity types, durations, and intensities on blood glucose levels. These studies, however, have had a great deal of variability in their outcomes. As a result, some of the recommended insulin adjustments and carbohydrate intake for exercise and physical activity remain vague, and a relatively high level of motivation is still necessary for developing the confidence required to be habitually physically active. It is also of note that some of the types of exercise now recommended for general health in individuals with type 1 diabetes (lifting weights, high-intensity interval training) are modalities that have historically been reserved for athletes and may be approached with trepidation by those who simply wish to be physically active for health.

Early Studies of Exercise in Diabetes

Prior to the discovery of insulin and the development of a better understanding of diabetes pathology, early studies examining exercise in individuals with diabetes were divided on its benefits for this population.[25] Some studies reported benefits for those with "moderate diabetes", yet others stated that exercise seemed to do little for those with "severe diabetes".[25] While early studies recognized that exercise was beneficial at decreasing the amount of glucose in the urine of the patient, it was not until 1926 that R.D. Lawrence (who was both a patient and a physician) recognized the link between insulin treatment and hypoglycemia during exercise in patients with type 1 diabetes.[26] Based on a clinical experiment with one patient and clinical experience with two others, Lawrence recommended that insulin dose be largely reduced both before and after exercise, and that food intake is increased on days where exercise is performed. In spite of substantial advancements in insulin formulations and delivery systems since then, this advice is still consistent with insulin adjustment and carbohydrate intake recommendations currently given to individuals with type 1 diabetes who undertake exercise and physical activity.

The fine-tuning of this advice has been ongoing now for decades as new insulins and insulin delivery systems have been developed. Where endogenous insulin levels would normally decline within minutes of starting exercise, the extended half-life of exogenous insulin results in higher than desired circulating insulin levels during exercise in those with type 1 diabetes. As a result, low- to moderate-intensity exercise has been associated with rapid declines in blood glucose, attributed to an insulin-induced lack of glucose production in spite of a marked increase in glucose uptake by the exercising muscle.[27] The consistency with which low to moderate-intensity aerobic exercise leads to a decline in blood glucose when individuals with type 1 diabetes are active in the post-prandial state has been universally recognized, and attempts have been made to associate specific insulin adjustments with particular intensities of aerobic exercise.[27–35] While the exact size and timing of the decrease in insulin administration vary greatly among individuals, the importance of reducing insulin dosage well in advance of exercise is almost unanimously recognized.[35–39] In situations where a decrease in insulin prior to activity is not possible, carbohydrate supplementation is almost inevitable, especially if the activities last longer than 20 mins.[40]

The Importance of Intensity

For many individuals with type 1 diabetes, the increase in carbohydrate intake to prevent hypoglycemia during moderate aerobic exercise decreases its potential weight and blood glucose management benefits. Efforts have, therefore, been made to find an alternative to carbohydrate consumption when exercise cannot be sufficiently planned in advance for insulin corrections, or where insulin corrections have not provided enough protection against declines in blood glucose. While counterintuitive at first, due to the greater amount of energy expended, increasing the intensity of the activities performed can have a protective effect against declines in blood glucose.

Over the last decade, there has been a substantial number of studies published emphasizing the impact of high intensity or anaerobic exercise (either in the form of intermittent intervals or as resistance exercise) on blood glucose levels in individuals with type 1 diabetes.[41–50] The increase in blood glucose that occurs with anaerobic activity had been well documented by studies of sustained high-intensity activity in participants with type 1 diabetes in the 1980s and 1990s.[51–55] This phenomenon during sustained high-intensity exercise is generally attributed to a catecholamine-induced increase in the rate of glucose appearance through hepatic glycogenolysis that is disproportionate to the rate of glucose uptake by the contracting muscle.[51,55,56]

The mechanism, while producing similar results, may be slightly different where much shorter, very intense bursts of activity are concerned. Two studies using labeled glucose to observe glucose rate of appearance and disappearance during and after a 10-s sprint in individuals with type 1 diabetes (under basal insulinaemic conditions) showed that, rather than a large increase in the rate of appearance, the increase in blood glucose concentration was in fact the result of a sharp decline in glucose uptake by the muscle after these very short, very intense bursts.[57,58] Regardless of the mechanism, these data became the basis for several studies of high intensity interval exercise (where low- to moderate-intensity aerobic activity are interrupted by occasional bouts of high- to very high-intensity activity) in individuals with type 1 diabetes. Most of these studies concluded that the inclusion of high-intensity bouts was protective against declines in blood glucose during exercise, compared to exercise sessions where no high-intensity bouts were included.[29,44,45,47,48,58] Similarly, weight lifting, another form of anaerobic exercise, has been associated with a protective effect against declines in blood glucose when combined with aerobic exercise.[59] Whether or not these types of training decrease the risk of hypoglycemia in the hours after activity completion is still under dispute.[45,46,59,60] It is also unclear whether or not this protective effect is diminished by undertaking high-intensity interval exercise under periods of peak insulin action. Overall, these findings have provided additional exercise safety tools for individuals with type 1 diabetes, which may serve to increase exercise confidence and uptake in this population.

Current Physical Activity/Exercise Recommendations

The last 3 years have led to the production of a variety of resources for exercise and physical activity in type 1 diabetes to be used by clinicians and patients alike. Both the American Diabetes Association[38] and the American College of Sports Medicine[39] have produced evidence-based recommendations around what type of exercise and physical activity to perform for people with type 1 diabetes, along with strategies for insulin dosage and carbohydrate intake to mitigate the risk of hypoglycemia. Similar to the exercise and physical activity guidelines for the general public,[61,62] individuals with type 1 diabetes are encouraged to perform 150 minutes or more of moderate to vigorous intensity activity every week. These minutes should be spread out over at least 3 days with no more than two consecutive days without activity. It is also recommended that 2–3 sessions per week of resistance exercise be included. The evidence behind these recommendations, however, is rated as mostly B or C grade for individuals with type 1 diabetes,[38] as there is a paucity of well-implemented randomized controlled trials of exercise in this population.

While the data supporting the long-term glycemic benefits of exercise in individuals with type 1 diabetes may be lacking, there have been several acute studies in the past 30 years examining the impact of exercise intensity, carbohydrate intake, and adjustments to insulin dosage (both using insulin pumps and multiple daily injections of insulin) in order to maximize exercise and physical activity safety. In 2017, these studies were reviewed by an expert group to produce a consensus statement entitled “Exercise Management in Type 1 Diabetes”.[37] To date, this publication offers the most detailed exercise safety guidelines available to the athlete or active individual with type 1 diabetes, including advice for insulin dosage management, dietary management, and hydration for specific levels of blood glucose, relative to different intensities and durations of exercise. However, it should still be noted that most of the studies on which this advice is based were performed on young, fit, males, and do not take into account potential age-[63] and sex-related[63,64] differences in exercise responses. As such, it is still advisable to individually tailor exercise and physical activity recommendations to the individual.

In addition to adjusting insulin dosage and increasing carbohydrate intake, several added safety guidelines have been provided for exercise in individuals with type 1 diabetes. It is recommended that they avoid injecting insulin into muscles that are about to be used for their activity, as this can speed up the rate of absorption and subsequently increase the risk of hypoglycemia.[65] An awareness of prior hypoglycemic events is highlighted, as having low blood glucose can blunt the body's counter regulatory response to rapidly decreasing blood glucose for at least 24 hrs.[66] Temperature may also play a role, with cool conditions delaying insulin delivery and increasing the risk of hyperglycemia, while warm conditions will have the opposite effect.[67] As outlined above, several exercise guidelines also recommend the inclusion of either resistance exercise, or high-intensity intervals, with aerobic exercise, as the combination seems to blunt the declines in blood glucose generally observed during aerobic exercise.[37–39] In addition, recent studies not included in current guidelines have shown that fasting resistance exercise[68] and high-intensity intermittent exercise,[69] may result in increases in blood glucose, where the same activity performed in the fed state later in the day could result in a decline in blood glucose levels. The same has also been found of aerobic exercise.[70] This phenomenon has been attributed to both the lower amount of insulin in circulation from a lack of meal-related bolus insulin, as well as higher concentrations of growth hormone and cortisol, which may promote lipids as a fuel source and thereby spare blood glucose during exercise.[68–70] Taken together, exercising before breakfast, may be advisable for active individuals with type 1 diabetes who are struggling with hypoglycemia, or are held back in their activities by the fear of hypoglycemia.

In spite of the availability of more detailed exercise safety advice than ever before, a one-size-fits-all set of recommendations is not currently possible. The available evidence is generally provided from studies involving small sample sizes (often fewer than 15 participants), and blood glucose responses show a great deal of variation. Overall, it can be recommended that individuals with type 1 diabetes treat their exercise like a science experiment: the key to success is making small changes to one variable at time, while taking very detailed notes until an effective combination is found. This will include making alterations in the type, timing and intensity of exercise, along with devising strategies for insulin dosage and carbohydrate intake before, during and after exercise. Fortunately, research has provided very sound suggestions on which approaches should be tried, and, in many cases, evidence to explain the observed outcomes.

The Role of Technological Improvements

When blood glucose meters for home use were first marketed in the early 1980s they revolutionized diabetes care. Rapid progress in glucose monitoring technology ensued, with meters becoming smaller, faster and more accurate, both in the target range (4–10 mmol/L) as well as above and below it.[71] Instead of a daily urine test providing little to no information on blood glucose excursions, individuals with type 1 diabetes had the ability to check blood glucose more frequently to provide a rough estimate of trends throughout the day. Compared to the conventional treatment of the day (one or two injections of insulin with once daily urine or blood glucose testing) the Diabetes Control and Complications Trial (1983–1993) showed that an increase in insulin injections (three or more per day) and self-monitoring of blood glucose four or more times per day using the newly developed home meters improved blood glucose control and decreased diabetes-related complications (cardiovascular disease, nephropathy, retinopathy and neuropathy).[72] Presumably, these meters also improved the ability of those with diabetes to undertake exercise and physical activity safely, as more information about pre- and post-exercise blood glucose levels was obtainable.

Just over twenty years later the first continuous glucose monitoring systems (CGM) became commercially available. For years these systems have modernized the field of exercise research for individuals with type 1 diabetes.[73] Where previous studies were either limited to a small window post-exercise, or required substantial funding and cooperation from participants to arrange overnight hospital stays, CGM systems allowed blood glucose data points to be collected every 5 mins for days at a time. Sensors for some of the original systems were wearable for up to 3 days. Some current systems have sensors approved for up to 14 days of wear. The use of these systems in exercise studies involving individuals with type 1 diabetes has improved the level of awareness around post-exercise and nocturnal hypoglycemia associated with different types, timing, and intensity of exercise.[73] Recent consensus recommendations on time in range for specific diabetes populations, as measured by CGM, will also make it easier to compare among exercise studies moving forward.[74]

For many athletes and active individuals with type 1 diabetes, the combination of CGM and faster-acting insulin formulations has vastly improved exercise safety. Where insulin treatment formerly involved mostly one or two injections of medium- to long-acting insulin on a daily basis, newer insulins allow for either multiple daily injections (generally one longer acting basal insulin with shorter-acting bolus insulin for snacks, meals and corrections) or infusion of fast-acting insulin using an insulin pump. As such, people with type 1 diabetes wishing to be more physically active are more easily able to plan ahead and aim for a lower level of circulating insulin during their physically active times, which, as previously discussed, is essential in the prevention of exercise-induced hypoglycemia. In addition, real-time CGM devices allow the exerciser to monitor changes in blood glucose through viewing both real-time blood glucose concentrations and trend arrows showing both the direction and rate of change of blood glucose levels. In one small, observational study, the use of both insulin pumps and real-time CGM over a 3-month period led to a significant reduction in mean glucose levels, and a decreased frequency of hyperglycemia in active individuals with type 1 diabetes.[75] Another recent study[76] of exercise in individuals with type 1 diabetes involving experiential learning for both patients and health-care providers demonstrated that CGM is a valuable tool to learn about blood glucose changes during exercise. In qualitative interviews, patients in this study also described the CGM as a safety net, and explained that it improved their ability to manage blood glucose during exercise without overcorrecting.

While some of the first studies of exercise involving CGM found that the accuracy of the sensors decreased during exercise (often attributed to sensor lag),[77,78] the newer sensors seem to be performing well during both moderate aerobic[79–81] and high-intensity interval[79–81] exercises. As most of these devices can also be equipped with alarms set to specific blood glucose thresholds, active individuals with type 1 diabetes can be notified when their blood glucose concentration is reaching an unsafe level both during exercise and overnight while asleep. As these devices also come with the ability to download several days' worth of data per sensor, along with providing access to online tools for assessing them, the user can make changes to their diet, insulin regime and physical activity/training schedules based on the large amount of data which is now available to them.

Future Possibilities

Improvements in sensor accuracy have helped in developing technologies where CGM can be directly linked to an insulin pump, allowing the real-time data from the CGM to assist individuals with type 1 diabetes in making decisions about their insulin delivery. These technologies now include insulin pumps that will suspend insulin delivery automatically when low blood glucose levels are detected, or even suspend insulin when low glucose levels are predicted.[82] These technologies are steps along the road to creating a completely closed-loop system, or artificial pancreas, which is able to independently monitor and control blood glucose levels in individuals with type 1 diabetes. Both single hormone (insulin only,[83–87] including faster-acting insulin[88]) and dual hormone (insulin and its antagonist glucagon)[86,89] systems are currently being tested in an exercise context.

One such single-hormone closed-loop system has recently become commercially available.[90] Overall, data on closed-loop systems show a clear advantage over conventional sensor-augmented insulin pumps with respect to decreasing hypoglycemia and increasing the amount of time in target blood glucose range.[91,92] There are still, however, some concerns about the ability of these systems to perform adequately during exercise due to some of the current gaps in the type 1 diabetes and exercise literature.[93–95] Most studies involving single hormone closed-loop systems have found similar results in sensor-augmented insulin pump therapy (where the user makes insulin delivery decisions) with respect to time in target for blood glucose concentration, and time in hypoglycemia.[83,84,87] Conversely, dual hormone closed-loop systems (which most closely replicate pancreatic function) have shown superiority over sensor-augmented insulin pumps[89] and single-hormone closed-loop systems[86] in small studies (n ≤ 21 participants) of aerobic exercise. With further improvement in algorithms and sensor accuracy, the type 1 diabetes community is hopeful that fear of hypoglycemia will no longer be a barrier to exercise and physical activity, as closed-loop systems should come close to eliminating the risk entirely.

Pancreatic islet transplantation is another advanced treatment option available to select individuals with type 1 diabetes who meet rigorous eligibility criteria.[96] This procedure, which is still considered experimental by most, involves the surgical transplantation of donor islet cells into the liver of the recipient. The procedure can restore both insulin secretion[97,98] and glucagon release[99,100] in the face of changes in blood glucose. One study comparing blood glucose responses to exercise in islet transplant recipients compared to matched controls without diabetes[101] showed that while blood glucose levels still declined during exercise, the risk of hypoglycemia in the transplant recipients was no greater than in the nondiabetic control participants. A more extreme example of athletic success after islet transplantation can be seen in a case report outlining the absence of hypoglycemia in an ultra-marathon endurance runner during training and competition post-transplant.[102] In spite of these successes, several challenges still prevent widespread access to this treatment including the availability of donor islets (especially in light of the fact that more than one transplant is often needed to achieve exogenous insulin independence) and the need for lifelong immunosuppression post-transplant.[103]

Conclusion

While blood glucose management around physical activity and exercise can still be a challenge for individuals with type 1 diabetes, the availability of information, tools and resources to overcome this hurdle has vastly improved over the past 50 years. In addition to a greater awareness of the benefits of exercise and physical activity in the prevention and management of diabetes-related complications, the ability to better understand and monitor blood glucose fluctuations during and after exercise continues to ameliorate exercise and physical activity safety for individuals with type 1 diabetes. It is also likely that these advancements can be credited, in some part, for the increase in the number of elite athletes with type 1 diabetes competing in both high-level amateur and professional sports.[104] The substantial advances in diabetes treatment and the understanding of physical activity and exercise are such that these are no longer viewed as risks to be avoided but rather as an essential part of health and wellness for people with type 1 diabetes.

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References

1. Schram MT, Chaturvedi N, Fuller JH, Stehouwer CD, Group EPCS. Pulse pressure is associated with age and cardiovascular disease in type 1 diabetes: the Eurodiab Prospective Complications Study. *J Hypertens*. 2003;21(11):2035–2044. doi:10.1097/00004872-200311000-00012
2. Soedamah-Muthu SS, Fuller JH, Mulnier HE, Raleigh VS, Lawrenson RA, Colhoun HM. High risk of cardiovascular disease in patients with type 1 diabetes in the UK: a cohort study using the general practice research database. *Diabetes Care*. 2006;29(4):798–804. doi:10.2337/diacare.29.04.06.dc05-1433
3. Larsson SC, Wallin A, Hakansson N, Stackelberg O, Back M, Wolk A. Type 1 and type 2 diabetes mellitus and incidence of seven cardiovascular diseases. *Int J Cardiol*. 2018;262:66–70. doi:10.1016/j.ijcard.2018.03.099
4. Secrest AM, Becker DJ, Kelsey SF, Laporte RE, Orchard TJ. Cause-specific mortality trends in a large population-based cohort with long-standing childhood-onset type 1 diabetes. *Diabetes*. 2010;59(12):3216–3222. doi:10.2337/db10-0862
5. Jansson RW, Hufthammer KO, Krohn J. Diabetic retinopathy in type 1 diabetes patients in Western Norway. *Acta Ophthalmol*. 2018;96(5):465–474. doi:10.1111/aos.2018.96.issue-5
6. Dorman JS, Laporte RE, Kuller LH, et al. The Pittsburgh insulin-dependent diabetes mellitus (IDDM) morbidity and mortality study. Mortality results. *Diabetes*. 1984;33(3):271–276. doi:10.2337/diab.33.3.271
7. Hicks CW, Selvin E. Epidemiology of peripheral neuropathy and lower extremity disease in diabetes. *Curr Diab Rep*. 2019;19(10):86. doi:10.1007/s11892-019-1212-8
8. Shah VN, Harrall KK, Shah CS, et al. Bone mineral density at femoral neck and lumbar spine in adults with type 1 diabetes: a meta-analysis and review of the literature. *Osteoporos Int*. 2017;28(9):2601–2610. doi:10.1007/s00198-017-4097-x
9. Krause MP, Riddell MC, Hawke TJ. Effects of type 1 diabetes mellitus on skeletal muscle: clinical observations and physiological mechanisms. *Pediatr Diabetes*. 2011;12(4 Pt 1):345–364. doi:10.1111/j.1399-5448.2010.00699.x
10. Tikkanen-Dolenc H, Waden J, Forsblom C, et al. Frequent and intensive physical activity reduces risk of cardiovascular events in type 1 diabetes. *Diabetologia*. 2017;60(3):574–580. doi:10.1007/s00125-016-4189-8
11. Bohn B, Herbst A, Pfeifer M, et al. Impact of physical activity on glycemic control and prevalence of cardiovascular risk factors in adults with type 1 diabetes: a cross-sectional multicenter study of 18,028 patients. *Diabetes Care*. 2015;38(8):1536–1543. doi:10.2337/dc15-0030
12. Tielemans SM, Soedamah-Muthu SS, De Neve M, et al. Association of physical activity with all-cause mortality and incident and prevalent cardiovascular disease among patients with type 1 diabetes: the EURODIAB prospective complications study. *Diabetologia*. 2013;56(1):82–91. doi:10.1007/s00125-012-2743-6
13. Waden J, Forsblom C, Thorn LM, et al. Physical activity and diabetes complications in patients with type 1 diabetes: the Finnish Diabetic Nephropathy (FinnDiane) study. *Diabetes Care*. 2008;31(2):230–232. doi:10.2337/dc07-1238
14. Mason NJ, Jenkins AJ, Best JD, Rowley KG. Exercise frequency and arterial compliance in non-diabetic and type 1 diabetic individuals. *Eur J Cardiovasc Prev Rehabil*. 2006;13(4):598–603. doi:10.1097/01.hjr.0000216546.07432.b2
15. Pongrac Barlovic D, Tikkanen-Dolenc H, Groop PH. Physical activity in the prevention of development and progression of kidney disease in type 1 diabetes. *Curr Diab Rep*. 2019;19(7):41. doi:10.1007/s11892-019-1157-y
16. Kriska AM, LaPorte RE, Patrick SL, Kuller LH, Orchard TJ. The association of physical activity and diabetic complications in individuals with insulin-dependent diabetes mellitus: the Epidemiology of Diabetes Complications Study–VII. *J Clin Epidemiol*. 1991;44(11):1207–1214. doi:10.1016/0895-4356(91)90153-Z
17. Moy CS, Songer TJ, LaPorte RE, et al. Insulin-dependent diabetes mellitus, physical activity, and death. *Am J Epidemiol*. 1993;137(1):74–81. doi:10.1093/oxfordjournals.aje.a116604
18. LaPorte RE, Dorman JS, Tajima N, et al. Pittsburgh Insulin-dependent Diabetes Mellitus Morbidity and Mortality study: physical activity and diabetic complications. *Pediatrics*. 1986;78(6):1027–1033.
19. Chimen M, Kennedy A, Nirantharakumar K, Pang TT, Andrews R, Narendran P. What are the health benefits of physical activity in type 1 diabetes mellitus? A literature review. *Diabetologia*. 2012;55(3):542–551. doi:10.1007/s00125-011-2403-2

20. Yardley JE, Hay J, Abou-Setta AM, Marks SD, McGavock J. A systematic review and meta-analysis of exercise interventions in adults with type 1 diabetes. *Diabetes Res Clin Pract*. 2014;106 (3):393–400. doi:10.1016/j.diabres.2014.09.038
21. Yardley JE, Kenny GP, Perkins BA, et al. Resistance versus aerobic exercise: acute effects on glycemia in type 1 diabetes. *Diabetes Care*. 2013;36(3):537–542. doi:10.2337/dc12-0963
22. Plotnikoff RC, Taylor LM, Wilson PM, et al. Factors associated with physical activity in Canadian adults with diabetes. *Med Sci Sports Exerc*. 2006;38(8):1526–1534. doi:10.1249/01.mss.0000228937.86539.95
23. McCarthy MM, Whittemore R, Grey M. Physical activity in adults with type 1 diabetes. *Diabetes Educ*. 2016;42(1):108–115. doi:10.1177/0145721715620021
24. Brazeau AS, Rabasa-Lhoret R, Strychar I, Mircescu H. Barriers to physical activity among patients with type 1 diabetes. *Diabetes Care*. 2008;31(11):2108–2109. doi:10.2337/dc08-0720
25. Allen F, Stillman E, Fitz R. *Total Dietary Regulation in the Treatment of Diabetes*. Ithaca, NY: Monographs of the Rockefeler Institute for Medical Research; 1919.
26. Lawrence RD. The effect of exercise on insulin action in diabetes. *Br Med J*. 1926;1(3406):648–650. doi:10.1136/bmj.1.3406.648
27. Zinman B, Murray FT, Vranic M, et al. Glucoregulation during moderate exercise in insulin treated diabetics. *J Clin Endocrinol Metab*. 1977;45(4):641–652. doi:10.1210/jcem-45-4-641
28. Rabasa-Lhoret R, Bourque J, Ducros F, Chiasson JL. Guidelines for premeal insulin dose reduction for postprandial exercise of different intensities and durations in type 1 diabetic subjects treated intensively with a basal-bolus insulin regimen (ultralente-lispro). *Diabetes Care*. 2001;24(4):625–630. doi:10.2337/diacare.24.4.625
29. Moser O, Tschakert G, Mueller A, et al. Effects of high-intensity interval exercise versus moderate continuous exercise on glucose homeostasis and hormone response in patients with type 1 diabetes mellitus using novel ultra-long-acting insulin. *PLoS ONE*. 2015;10(8):e0136489. doi:10.1371/journal.pone.0136489
30. Dube MC, Weisnagel SJ, Prud'homme D, Lavoie C. Exercise and newer insulins: how much glucose supplement to avoid hypoglycemia? *Med Sci Sports Exerc*. 2005;37(8):1276–1282. doi:10.1249/01.mss.0000174950.25188.36
31. Franc S, Daoudi A, Pochat A, et al. Insulin-based strategies to prevent hypoglycaemia during and after exercise in adult patients with type 1 diabetes on pump therapy: the DIABRASPORT randomized study. *Diabetes Obes Metab*. 2015;17(12):1150–1157. doi:10.1111/dom.2015.17.issue-12
32. Sonnenberg GE, Kemmer FW, Berger M. Exercise in type 1 (insulin-dependent) diabetic patients treated with continuous subcutaneous insulin infusion. Prevention of exercise induced hypoglycaemia. *Diabetologia*. 1990;33(11):696–703. doi:10.1007/BF00400572
33. West DJ, Morton RD, Bain SC, Stephens JW, Bracken RM. Blood glucose responses to reductions in pre-exercise rapid-acting insulin for 24 h after running in individuals with type 1 diabetes. *J Sports Sci*. 2010;28(7):781–788. doi:10.1080/02640411003734093
34. West DJ, Stephens JW, Bain SC, et al. A combined insulin reduction and carbohydrate feeding strategy 30 min before running best preserves blood glucose concentration after exercise through improved fuel oxidation in type 1 diabetes mellitus. *J Sports Sci*. 2011;29(3):279–289. doi:10.1080/02640414.2010.531753
35. Zaharieva DP, McGaugh S, Pooni R, Vienneau T, Ly T, Riddell MC. Improved open-loop glucose control with basal insulin reduction 90 minutes before aerobic exercise in patients with type 1 diabetes on continuous subcutaneous insulin infusion. *Diabetes Care*. 2019;42(5):824–831. doi:10.2337/dc18-2204
36. Roy-Fleming A, Taleb N, Messier V, et al. Timing of insulin basal rate reduction to reduce hypoglycemia during late post-prandial exercise in adults with type 1 diabetes using insulin pump therapy: a randomized crossover trial. *Diabetes Metab*. 2019;45 (3):294–300. doi:10.1016/j.diabet.2018.08.002
37. Riddell MC, Gallen IW, Smart CE, et al. Exercise management in type 1 diabetes: a consensus statement. *Lancet Diabetes Endocrinol*. 2017;5(5):377–390. doi:10.1016/S2213-8587(17)30014-1
38. Colberg SR, Sigal RJ, Yardley JE, et al. Physical activity/exercise and diabetes: a position statement of the american diabetes association. *Diabetes Care*. 2016;39(11):2065–2079. doi:10.2337/dc16-1728
39. Yardley JE, Colberg SR. Update on management of type 1 diabetes and type 2 diabetes in athletes. *Curr Sports Med Rep*. 2017;16(1):38–44. doi:10.1249/JSR.0000000000000327
40. Shetty VB, Fournier PA, Davey RJ, et al. The time lag prior to the rise in glucose requirements to maintain stable glycaemia during moderate exercise in a fasted insulinaemic state is of short duration and unaffected by the level at which glycaemia is maintained in Type 1 diabetes. *Diabet Med*. 2018;35(10):1404–1411. doi:10.1111/dme.2018.35.issue-10
41. Riddell MC, Pooni R, Yavelberg L, et al. Reproducibility in the cardiometabolic responses to high-intensity interval exercise in adults with type 1 diabetes. *Diabetes Res Clin Pract*. 2019;148:137–143. doi:10.1016/j.diabres.2019.01.003
42. Scott SN, Cocks M, Andrews RC, et al. High-intensity interval training improves aerobic capacity without a detrimental decline in blood glucose in people with type 1 diabetes. *J Clin Endocrinol Metab*. 2019;104(2):604–612. doi:10.1210/jc.2018-01309
43. Soon WHK, Guelfi KJ, Davis EA, Smith GJ, Jones TW, Fournier PA. Effect of combining pre-exercise carbohydrate intake and repeated short sprints on the blood glucose response to moderate-intensity exercise in young individuals with Type 1 diabetes. *Diabet Med*. 2019;36(5):612–619. doi:10.1111/dme.2019.36.issue-5
44. Guelfi KJ, Jones TW, Fournier PA. The decline in blood glucose levels is less with intermittent high-intensity compared with moderate exercise in individuals with type 1 diabetes. *Diabetes Care*. 2005;28(6):1289–1294. doi:10.2337/diacare.28.6.1289
45. Maran A, Pavan P, Bonsembiante B, et al. Continuous glucose monitoring reveals delayed nocturnal hypoglycemia after intermittent high-intensity exercise in nontrained patients with type 1 diabetes. *Diabetes Technol Ther*. 2010;12(10):763–768. doi:10.1089/dia.2010.0038
46. Iscoe KE, Riddell MC. Continuous moderate-intensity exercise with or without intermittent high-intensity work: effects on acute and late glycaemia in athletes with Type 1 diabetes mellitus. *Diabet Med*. 2011;28(7):824–832. doi:10.1111/j.1464-5491.2011.03274.x
47. Dube MC, Lavoie C, Weisnagel SJ. Glucose or intermittent high-intensity exercise in glargine/glulisine users with T1DM. *Med Sci Sports Exerc*. 2013;45(1):3–7. doi:10.1249/MSS.0b013e31826c6ad3
48. Campbell MD, West DJ, Bain SC, et al. Simulated games activity vs continuous running exercise: a novel comparison of the glycemic and metabolic responses in T1DM patients. *Scand J Med Sci Sports*. 2015;25(2):216–222. doi:10.1111/sms.2015.25.issue-2
49. Zaharieva D, Yavelberg L, Jamnik V, Cinar A, Turksoy K, Riddell MC. The effects of basal insulin suspension at the start of exercise on blood glucose levels during continuous versus circuit-based exercise in individuals with type 1 diabetes on continuous subcutaneous insulin infusion. *Diabetes Technol Ther*. 2017;19(6):370–378. doi:10.1089/dia.2017.0010
50. Zaharieva DP, Cinar A, Yavelberg L, Jamnik V, Riddell MC. No disadvantage to insulin pump off vs pump on during intermittent high-intensity exercise in adults with type 1 diabetes. *Can J Diabetes*. 2019. doi:10.1016/j.jcjd.2019.05.015

51. Purdon C, Brousson M, Nyveen SL, et al. The roles of insulin and catecholamines in the glucoregulatory response during intense exercise and early recovery in insulin-dependent diabetic and control subjects. *J Clin Endocrinol Metab*. 1993;76(3):566–573. doi:10.1210/jcem.76.3.8445012
52. Mitchell TH, Abraham G, Schiffrin A, Leiter LA, Marliss EB. Hyperglycemia after intense exercise in IDDM subjects during continuous subcutaneous insulin infusion. *Diabetes Care*. 1988;11(4):311–317. doi:10.2337/diacare.11.4.311
53. Sigal RJ, Fisher SJ, Halter JB, Vranic M, Marliss EB. Glucoregulation during and after intense exercise: effects of beta-adrenergic blockade in subjects with type 1 diabetes mellitus. *J Clin Endocrinol Metab*. 1999;84(11):3961–3971. doi:10.1210/jcem.84.11.6116
54. Sigal RJ, Fisher SJ, Manzon A, et al. Glucoregulation during and after intense exercise: effects of alpha-adrenergic blockade. *Metabolism*. 2000;49(3):386–394. doi:10.1016/S0026-0495(00)90374-3
55. Sigal RJ, Purdon C, Fisher SJ, Halter JB, Vranic M, Marliss EB. Hyperinsulinemia prevents prolonged hyperglycemia after intense exercise in insulin-dependent diabetic subjects. *J Clin Endocrinol Metab*. 1994;79(4):1049–1057. doi:10.1210/jcem.79.4.7962273
56. Marliss EB, Vranic M. Intense exercise has unique effects on both insulin release and its roles in glucoregulation: implications for diabetes. *Diabetes*. 2002;51(Suppl 1):S271–283. doi:10.2337/diabetes.51.2007.S271
57. Fahey AJ, Paramalingam N, Davey RJ, Davis EA, Jones TW, Fournier PA. The effect of a short sprint on postexercise whole-body glucose production and utilization rates in individuals with type 1 diabetes mellitus. *J Clin Endocrinol Metab*. 2012;97(11):4193–4200. doi:10.1210/jc.2012-1604
58. Bally L, Zueger T, Buehler T, et al. Metabolic and hormonal response to intermittent high-intensity and continuous moderate intensity exercise in individuals with type 1 diabetes: a randomised crossover study. *Diabetologia*. 2016;59(4):776–784. doi:10.1007/s00125-015-3854-7
59. Yardley JE, Kenny GP, Perkins BA, et al. Effects of performing resistance exercise before versus after aerobic exercise on glycemia in type 1 diabetes. *Diabetes Care*. 2012;35(4):669–675. doi:10.2337/dc11-1844
60. Rempel M, Yardley JE, MacIntosh A, et al. Vigorous intervals and hypoglycemia in type 1 diabetes: a randomized cross over trial. *Sci Rep*. 2018;8(1):15879. doi:10.1038/s41598-018-34342-6
61. Canadian Society for Exercise Physiology. *Canadian physical activity guidelines for adults – 18–64 years*. Ottawa, Ontario; 2011. Available at: http://csep.ca/CMFiles/Guidelines/CSEP_PAGuidelines_0-65plus_en.pdf.
62. Garber CE, Blissmer B, Deschenes MR, et al. American College of Sports Medicine position stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. *Med Sci Sports Exerc*. 2011;43(7):1334–1359. doi:10.1249/MSS.0b013e318213fefb
63. Yardley JE, Brockman NK, Bracken RM. Could age, sex and physical fitness affect blood glucose responses to exercise in type 1 diabetes? *Front Endocrinol (Lausanne)*. 2018;9:674. doi:10.3389/fendo.2018.00674
64. Brockman NK, Yardley JE. Sex-related differences in fuel utilization and hormonal response to exercise: implications for individuals with type 1 diabetes. *Appl Physiol Nutr Metab*. 2018;43(6):541–552. doi:10.1139/apnm-2017-0559
65. Frid A, Ostman J, Linde B. Hypoglycemia risk during exercise after intramuscular injection of insulin in thigh in IDDM. *Diabetes Care*. 1990;13(5):473–477. doi:10.2337/diacare.13.5.473
66. Davis SN, Galassetti P, Wasserman DH, Tate D. Effects of antecedent hypoglycemia on subsequent counterregulatory responses to exercise. *Diabetes*. 2000;49(1):73–81. doi:10.2337/diabetes.49.1.73
67. Ronnemaa T, Koivisto VA. Combined effect of exercise and ambient temperature on insulin absorption and postprandial glycemia in type I patients. *Diabetes Care*. 1988;11(10):769–773. doi:10.2337/diacare.11.10.769
68. Toghi-Eshghi SR, Yardley JE. Morning (fasting) vs afternoon resistance exercise in individuals with type 1 diabetes: a randomized crossover study. *J Clin Endocrinol Metab*. 2019;104(11):5217–5224. doi:10.1210/jc.2018-02384
69. Yardley J. Effect of morning (fasting) versus afternoon high intensity intermittent exercise on blood glucose in type 1 diabetes. *Diabetes*. 2019;68(Suppl 1):751–P. doi:10.2337/db19-751-P
70. Ruegemer JJ, Squires RW, Marsh HM, et al. Differences between prebreakfast and late afternoon glycemic responses to exercise in IDDM patients. *Diabetes Care*. 1990;13(2):104–110. doi:10.2337/diacare.13.2.104
71. Clarke SF, Foster JR. A history of blood glucose meters and their role in self-monitoring of diabetes mellitus. *Br J Biomed Sci*. 2012;69(2):83–93. doi:10.1080/09674845.2012.12002443
72. DCCT Study Group. The Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC Publications). Available from: https://portal.bsc.gwu.edu/documents/82966/28932550/2018+NOV+21+DCCT-EDIC+P+and+P+List.pdf/961d1dfd-4db7-4759-a4e5-5f35da56a35a. Accessed October 10, 2019.
73. Houlder SK, Yardley JE. Continuous glucose monitoring and exercise in type 1 diabetes: past, present and future. *Biosensors (Basel)*. 2018;8:3.
74. Battelino T, Danne T, Bergenstal RM, et al. Clinical targets for continuous glucose monitoring data interpretation: recommendations from the international consensus on time in range. *Diabetes Care*. 2019;42(8):1593–1603. doi:10.2337/dci19-0028
75. Adamo M, Codella R, Casiraghi F, et al. Active subjects with autoimmune type 1 diabetes have better metabolic profiles than sedentary controls. *Cell Transplant*. 2017;26(1):23–32. doi:10.3727/096368916X693022
76. Dyck RA, Kleinman NJ, Funk DR, Yeung RO, Senior P, Yardley JE. We can work (it) out together: type 1 diabetes boot camp for adult patients and providers improves exercise self-efficacy. *Can J Diabetes*. 2018;42(6):619–625. doi:10.1016/j.jcjd.2018.02.006
77. Radermecker RP, Fayolle C, Brun JF, Bringer J, Renard E. Accuracy assessment of online glucose monitoring by a subcutaneous enzymatic glucose sensor during exercise in patients with type 1 diabetes treated by continuous subcutaneous insulin infusion. *Diabetes Metab*. 2013;39(3):258–262. doi:10.1016/j.diabet.2012.12.004
78. Yardley JE, Sigal RJ, Kenny GP, Riddell MC, Lovblom LE, Perkins BA. Point accuracy of interstitial continuous glucose monitoring during exercise in type 1 diabetes. *Diabetes Technol Ther*. 2013;15(1):46–49. doi:10.1089/dia.2012.0182
79. Bally L, Zueger T, Pasi N, Carlos C, Paganini D, Stettler C. Accuracy of continuous glucose monitoring during differing exercise conditions. *Diabetes Res Clin Pract*. 2016;112:1–5. doi:10.1016/j.diabres.2015.11.012
80. Moser O, Mader JK, Tschakert G, et al. Accuracy of continuous glucose monitoring (cgm) during continuous and high-intensity interval exercise in patients with type 1 diabetes mellitus. *Nutrients*. 2016;8:8. doi:10.3390/nu8080489
81. Aberer F, Hajnsek M, Rumpler M, et al. Evaluation of subcutaneous glucose monitoring systems under routine environmental conditions in patients with type 1 diabetes. *Diabetes Obes Metab*. 2017;19(7):1051–1055. doi:10.1111/dom.12907
82. Battelino T, Nimri R, Dovc K, Phillip M, Bratina N. Prevention of hypoglycemia with predictive low glucose insulin suspension in children with type 1 diabetes: a randomized controlled trial. *Diabetes Care*. 2017;40(6):764–770. doi:10.2337/dc16-2584

83. Dovc K, Macedoni M, Bratina N, et al. Closed-loop glucose control in young people with type 1 diabetes during and after unannounced physical activity: a randomised controlled crossover trial. *Diabetologia*. 2017;60:2157–2167. doi:10.1007/s00125-017-4395-z
84. Breton MD, Chernavvsky DR, Forlenza GP, et al. Closed-loop control during intense prolonged outdoor exercise in adolescents with type 1 diabetes: the artificial pancreas ski study. *Diabetes Care*. 2017;40(12):1644–1650. doi:10.2337/dc17-0883
85. Patel NS, Van Name MA, Cengiz E, et al. Mitigating reductions in glucose during exercise on closed-loop insulin delivery: the Ex-Snacks study. *Diabetes Technol Ther*. 2016;18(12):794–799. doi:10.1089/dia.2016.0311
86. Taleb N, Emami A, Suppere C, et al. Efficacy of single-hormone and dual-hormone artificial pancreas during continuous and interval exercise in adult patients with type 1 diabetes: randomised controlled crossover trial. *Diabetologia*. 2016;59(12):2561–2571. doi:10.1007/s00125-016-4107-0
87. Breton MD, Brown SA, Karvetski CH, et al. Adding heart rate signal to a control-to-range artificial pancreas system improves the protection against hypoglycemia during exercise in type 1 diabetes. *Diabetes Technol Ther*. 2014;16(8):506–511. doi:10.1089/dia.2013.0333
88. Dovc K, Piona C, Yesiltepe Mutlu G, et al. Faster compared with standard insulin aspart during day-and-night fully closed-loop insulin therapy in type 1 diabetes: a double-blind randomized crossover trial. *Diabetes Care*. 2019:dc190895. (in press). doi:10.2337/dc19-0895.
89. Jacobs PG, El Youssef J, Reddy R, et al. Randomized trial of a dual-hormone artificial pancreas with dosing adjustment during exercise compared with no adjustment and sensor-augmented pump therapy. *Diabetes Obes Metab*. 2016;18(11):1110–1119. doi:10.1111/dom.2016.18.issue-11
90. Saunders A, Messer LH, Forlenza GP. MiniMed 670G hybrid closed loop artificial pancreas system for the treatment of type 1 diabetes mellitus: overview of its safety and efficacy. *Expert Rev Med Devices*. 2019;1–9.
91. Bekiari E, Kitsios K, Thabit H, et al. Artificial pancreas treatment for outpatients with type 1 diabetes: systematic review and meta-analysis. *BMJ*. 2018;361:k1310. doi:10.1136/bmj.k1310
92. Weisman A, Bai JW, Cardinez M, Kramer CK, Perkins BA. Effect of artificial pancreas systems on glycaemic control in patients with type 1 diabetes: a systematic review and meta-analysis of outpatient randomised controlled trials. *Lancet Diabetes Endocrinol*. 2017;5(7):501–512. doi:10.1016/S2213-8587(17)30167-5
93. Colberg SR, Laan R, Dassau E, Kerr D. Physical activity and type 1 diabetes: time for a rewire? *J Diabetes Sci Technol*. 2015;9(3):609–618. doi:10.1177/1932296814566231
94. Riddell MC, Zaharieva DP, Yavelberg L, Cinar A, Jamnik VK. Exercise and the development of the artificial pancreas: one of the more difficult series of hurdles. *J Diabetes Sci Technol*. 2015;9(6):1217–1226. doi:10.1177/1932296815609370
95. Moser O, Yardley JE, Bracken RM. Interstitial glucose and physical exercise in type 1 diabetes: integrative physiology, technology, and the gap in-between. *Nutrients*. 2018;10:1. doi:10.3390/nu10010093
96. Shapiro AM, Lakey JR, Ryan EA, et al. Islet transplantation in seven patients with type 1 diabetes mellitus using a glucocorticoid-free immunosuppressive regimen. *N Engl J Med*. 2000;343(4):230–238. doi:10.1056/NEJM200007273430401
97. Ryan EA, Lakey JR, Paty BW, et al. Successful islet transplantation: continued insulin reserve provides long-term glycemic control. *Diabetes*. 2002;51(7):2148–2157. doi:10.2337/diabetes.51.7.2148
98. Rickels MR, Mueller R, Teff KL, Naji A. {beta}-Cell secretory capacity and demand in recipients of islet, pancreas, and kidney transplants. *J Clin Endocrinol Metab*. 2010;95(3):1238–1246. doi:10.1210/jc.2009-2289
99. Rickels MR, Schutta MH, Mueller R, et al. Islet cell hormonal responses to hypoglycemia after human islet transplantation for type 1 diabetes. *Diabetes*. 2005;54(11):3205–3211. doi:10.2337/diabetes.54.11.3205
100. Rickels MR, Peleckis AJ, Markmann E, et al. Long-term improvement in glucose control and counterregulation by islet transplantation for type 1 diabetes. *J Clin Endocrinol Metab*. 2016;101(11):4421–4430. doi:10.1210/jc.2016-1649
101. Yardley JE, Rees JL, Funk DR, Toghi-Eshghi SR, Boule NG, Senior PA. Effects of moderate cycling exercise on blood glucose regulation following successful clinical islet transplantation. *J Clin Endocrinol Metab*. 2019;104(2):493–502. doi:10.1210/jc.2018-01498
102. Codella R, Adamo M, Maffi P, Piemonti L, Secchi A, Luzi L. Ultra-marathon 100 km in an islet-transplanted runner. *Acta Diabetol*. 2017;54(7):703–706. doi:10.1007/s00592-016-0938-x
103. Vantyghem MC, de Koning EJP, Pattou F, Rickels MR. Advances in beta-cell replacement therapy for the treatment of type 1 diabetes. *Lancet*. 2019;394(10205):1274–1285. doi:10.1016/S0140-6736(19)31334-0
104. List of sportspeople with diabetes. Available from: https://en.wikipedia.org/wiki/List_of_sportspeople_with_diabetes. Accessed October 15, 2019.