Cycling for people with type 1 diabetes

Abstract
Cycling is increasing in popularity for both recreational and practical purposes. Marked changes in blood glucose are seen during and following cycling, with risk of hypoglycaemia. There is now an extensive body of clinical and research evidence to assist the clinician when advising the person with type 1 diabetes mellitus, to help people manage diabetes and exercise more effectively. Fortuitously, much of the research evidence is based on cycling.

Key words
diabetes; type 1 diabetes; cycling; insulin treatment; hypoglycaemia; insulin infusion pump therapy; continuous glucose monitoring

Introduction
Cycling has increased in popularity over the last few years, and anyone travelling around at the weekends cannot fail to be impressed by the sheer number of recreational cyclists, some of whom are somewhat unfairly described by the acronym MAMIL (middle-aged men in Lycra). Another powerful force in the development of cycling is the move towards sustainable transport. As the cost of the commute to and from work or education increases, and with the increase in safer dedicated cycle lanes, cycling becomes a rational choice for personal transport.

Where does this leave the person with type 1 diabetes? Strenuous physical activity may cause difficulties in maintaining glycaemic control which may make managing diabetes and cycling challenging. However, there is now an extensive body of clinical and research evidence to assist the clinician when advising the person with type 1 diabetes (T1DM) who wishes to cycle.

Exercise physiology in health
Cycling is predominantly an endurance or aerobic exercise. What this means is that the exercise is sub-maximal, and that fuels consumed during exercise are fully oxidised, rather than partly metabolised requiring excess post-exercise oxygen consumption. This does not mean that the exercising muscles are working completely aerobically, but does mean that any excess muscle lactate production from exercising muscle is taken up by less exercising muscles and by other tissues to be converted to glucose for storage or oxidation. It is helpful to think of the example of a cycling road race. If one imagines the Peloton crossing the plains during the Tour de France, the cyclists are working at the top of their aerobics capacity. They have achieved this through training which increases the cardiovascular capacity to deliver oxygen to predominantly the leg muscles, the capacity of the blood to carry oxygen, and the ability of the liver and kidney to uptake lactic acid. They will be oxidising relatively little glucose, instead relying on fuels derived from the fat stores. At the start of cycling the muscles use glucose as their primary fuel, derived from muscle glycogen stores. As these stores are depleted, a balance develops between hepatic glucose production and uptake by exercising muscle. This response is controlled by the endocrine system (Table 1). Exercise reduces insulin secretion through sympathetic nervous system activation and the change in the ratio of glucagon to insulin at the liver promotes hepatic glucose production. Exercise-induced translocation of GLUT-4 receptors to the cell surface enables increased muscle glucose uptake even with falling insulin levels.

Clearly, in some circumstances cycling can be anaerobic. Returning to our example of the road race, as the cyclists reach the challenging climb of the stage, the work increases, lactate production now exceeds uptake, and exercise must be limited. Even while global oxygen...
uptake may be sufficient, local muscle groups may have insufficient delivery, so that muscle is unable to utilise the full potential of the carbohydrate fuel available. Lactate acid production increases as a result of this and other fuels are utilised less. Lactate homeostasis is maintained with excess lactate production being taken up by other tissues. As workload increases, lactate acid production exceeds uptake (the lactate threshold), and blood lactate levels increase.\textsuperscript{6,7} Ultimately, exercise will be limited by rising lactate levels, but the tolerance to increased lactate levels to enable maximal performance does vary between individuals. Eventually, lactate levels rise to such a level which cannot be tolerated and the unpleasant symptoms of aching muscles, pounding heart and shortness of breath make it impossible to exercise any longer at that intensity.

Glucose production is increased by seven to eight times to achieve the required work output, with circulating catecholamines increasing to between 14 and 18 times their baseline level.\textsuperscript{8,9} High performing cyclists have a high lactate threshold and, when this is exceeded, have high lactate tolerance.

Physical training therefore increases physical fitness by increasing oxygen delivery to muscle through improved cardio-respiratory responses to exercise, increased glucose and fuel uptake into muscle and by improvements in lactate uptake by the liver, kidney and the other less exercising muscles. These adaptions combine to raise the lactate threshold. Ultimately, exercise capacity can be further increased by increasing the level of lactate tolerance. These principles are similar for people with or without T1DM.

### Effect of exercise on glycaemic control in type 1 diabetes

The endocrine and resultant metabolic responses during and following exercise are altered in T1DM (Table 2). These changes have been reviewed extensively but are summarised as follows.\textsuperscript{10} Injected insulin sits in subcutaneous depots, from where absorption continues or may actually increase during exercise. As a result there may be comparatively excessive levels relative to the glucose concentration. As previously described, exercise induces non-insulin dependent translocation of GLUT-4 receptors to the cell surface which increase muscle glucose uptake, even with low insulin levels. All parts of the counter-regulatory response to endurance exercise are impaired, and the insulin to glucagon ratio presented to the liver is inappropriately high, with glucose production not increasing adequately during exercise to cope with the increased fuel requirement. There is inappropriately high glucose uptake by non-exercising muscles and other tissues. The catecholamine and growth hormone responses to exercise are also deficient. This will reduce glucose production. As a result, during prolonged exercise, the relatively high ambient plasma insulin levels, increased non-insulin mediated glucose uptake when combined with a deficient counter-regulatory hormonal response will provoke a marked fall in blood glucose. Furthermore, there is less release of other fuels and so a person with T1DM tends to oxidize excessive glucose, rather than fatty acids or ketones, which may contribute to excess fatigue.

To some extent, the endurance cyclist has almost a similar endocrine state as the person with untreated T1DM, but does not accumulate glucose and ketone bodies because these are all oxidized. This suggests that the optimum management of people with T1DM during exercise to maximise performance and reduce the risk of hypoglycaemia may be to replicate this physiological hypo-insulinaemic state during exercise. However, insulin levels must be restored quickly to deal with post-exercise hyperglycaemia.

Intense exercise produces a greater counter-regulatory hormone response than sub-maximal endurance exercise in T1DM\textsuperscript{6,7,11–13} Intermittent high-intensity exercise is associated with a lesser fall in glucose than moderate exercise of a similar workload. When people with T1DM were exercised for 30 minutes by continuous sub-maximal exercise or with 4-second sprints performed every 2 minutes, the decline in blood glucose was less with the intense exercise.
Glucose levels remained stable during recovery, but continued to fall after sub-maximal exercise alone. The mechanism for this stabilisation of blood glucose levels appears to be mediated through increased secretion of catecholamines and growth hormone during early recovery after exercise.\textsuperscript{14}

Short periods of intense exercise performed before, or following, endurance exercise can also attenuate the decline in blood glucose that occurs following exercise. When a maximal 10-second cycling sprint was performed immediately following exercise of moderate intensity the fall in blood glucose was less in the 2 hours following exercise when compared to that observed following moderate-intensity exercise without the brief sprint. A similar protective effect is observed if the 10-second sprint is performed before continuous exercise.\textsuperscript{11,12}

This protective effect of high-intensity exercise seems to be lost in the late post-exercise period. Nocturnal hypoglycaemia is more frequent following intermittent high-intensity exercise than after moderate exercise. When glucose profiles were examined using continuous glucose monitoring during, and in the 20 hours after a 30-minute session of either intermittent high-intensity exercise or moderate-intensity exercise, glucose levels declined during both types of exercise. However, between midnight and 6:00 a.m. the glucose levels were significantly lower after the period of intermittent exercise, and the number of hypoglycaemic episodes was greater than after lower-intensity exercise.\textsuperscript{15}

Exogenous insulin treatment for T1DM therefore has significant effects on the endocrine response to exercise, and insulin levels may be inappropriate either during or following cycling. While blood glucose levels generally fall rapidly during cycling, there are some circumstances in which they may remain stable or even increase.

The interaction between hypoglycaemia and exercise

Hypoglycaemia can be difficult to detect during exercise as many of the symptomatic manifestations of hypoglycaemia (sweating and increased heart rate) are similar to those experienced by an exercising athlete. There are complex interactions between exercise and hypoglycaemia. Hypoglycaemia before cycling reduces the counter-regulatory hormone response with exercise, and thus must increase the risk of further hypoglycaemia.\textsuperscript{16} A person with TIDM who has experienced an episode of hypoglycaemia on the day before the period of exercise will therefore need to ingest more glucose to avoid developing hypoglycaemia during subsequent exercise.\textsuperscript{17}

In a similar way, exercise also impairs the counter-regulatory response and awareness of later hypoglycaemia.\textsuperscript{18,19} Epinephrine, pancreatic polypeptide, muscle sympathetic neural activity and endogenous glucose production were all significantly lower during hypoglycaemia induced on the subsequent day, after 90 minutes of moderate sub-maximal exercise, in comparison with hypoglycaemia induced in control subjects with TIDM who had rested. This exercise-induced counter-regulatory failure can occur very rapidly, increasing the risk of hypoglycaemia developing within hours in TIDM.\textsuperscript{19} It is noteworthy that the risk of hypoglycaemia in males following exercise seems to be higher than that for females as the counter-regulatory response to exercise following hypoglycaemia is relatively preserved in women.\textsuperscript{20}

Hypoglycaemia is also more likely to occur and less likely to be recognised during sleep following a preceding period of exercise. One of the earliest observations was that hypoglycaemia occurs 6–15 hours after the completion of unusually strenuous exercise and was nocturnal. In more than half the cases the hypoglycaemia resulted in loss of consciousness or seizures and necessitated treatment with subcutaneous glucagon or intravenous glucose and/or emergency medical assistance. Hypoglycaemia was not limited to people with good or strict glycaemic control and often occurred after a single bout of exercise in individuals who were unaccustomed to physical activity or in athletic patients who were making the transition from an untrained to a trained state.\textsuperscript{21} The mechanism for this increased risk of nocturnal hypoglycaemia is multifactorial, being the result of the combination of increased nocturnal glucose disposal into skeletal muscle,\textsuperscript{22} and impaired counter-regulatory response to hypoglycaemia following exercise. This risk is greater following alcohol ingestion,\textsuperscript{23,24} and hypoglycaemia is less likely to be observed and treated in those who sleep alone, and is potentially life threatening.\textsuperscript{25}

Strategies to maintain euglycaemia during and after exercise

What advice should be given to people who plan to cycle? The first advice must be to reduce day-to-day variation in insulin therapy with review of injection techniques, and to improve insulin dosage relative to carbohydrate intake. The interview should then explore the detail of any planned cycling intensity and duration, along with relationship to insulin treatment and food intake. With this information, prediction of likely change in glucose levels with planned cycling can be made.

Several strategies can be adopted to maintain euglycaemia during and following exercise (Table 3). The mainstay of management remains ingestion of carbohydrate before and during exercise. It is important not to over-replace, as this results in hyperglycaemia. Simpler forms of carbohydrate, such as glucose, can be ingested regularly during exercise in an accessible form.\textsuperscript{26–32} Evidence suggests that the ability to absorb glucose during exercise is limited to as little as 60g/hour.\textsuperscript{33} Typically a 70kg adult may be ingesting 20g of glucose every 20 minutes during exercise.\textsuperscript{34} Where exercise is for less than 1 hour, simple carbohydrates should be consumed. When exercise is more prolonged, more palatable complex foods can be ingested.

People taking multiple daily insulin (MDI) injections can adjust their pre-exercise bolus insulin dose and take extra carbohydrate during exercise to reduce the risk of hypoglycaemia.\textsuperscript{28,35,36} Lower pre-meal insulin doses were associated with a lower incidence of exercise-induced hypoglycaemia, but with
some post-prandial hyperglycaemia. As a result, this is really only useful if exercise is to take place within 90 minutes of the ultra short-acting insulin dose.

Continuous subcutaneous insulin infusion (CSII) offers the capacity to modify the basal insulin rate by small increments and to obtain an effect relatively quickly. The subcutaneous reservoir of insulin is very small, and CSII provides an ability to give multiple additional bolus doses of insulin without needing to give additional injections. With an insulin pump, it is possible to reduce or suspend insulin infusion during exercise. We have found CSII therapy very useful in cyclists and there are some data to support this. In an observational study of aerobic exercise (cycling or running at 60% peak aerobic capacity) and during 6 hours post exercise. Both MDI and CSII groups had similar reductions in glucose levels during exercise. However, responses in early and late recovery differed, with those using MDI having greater increases in glucose throughout recovery compared with individuals with CSII. Two-thirds of the MDI patients experienced late-onset post-exercise hyperglycaemia, compared with only a few of the CSII patients.

The use of CSII seems to help limit post-exercise hyperglycaemia compared with MDI therapy and was not associated with increased risk for post-exercise late-onset hypoglycaemia. There are few data currently available to indicate by how much the insulin infusion rates may have to be modified or the most appropriate time at which these changes in rate should be made. However, our observations are that a large reduction in insulin infusion rate or even complete suspension is required at least 30 minutes before commencing prolonged cycling. For people treated with CSII therapy, post-exercise adjustment of the basal rate of insulin infusion is feasible. From clinical experience, in people who take exercise less frequently than on alternate days, nocturnal hypoglycaemia can be limited without compromising overall glycaemic control (including morning fasting glucose readings). This is done by reducing the basal CSII rate during the night after the exercise. Following 60 minutes of exercise, the most effective rate adjustment appears to be a reduction in the basal insulin infusion rate of 25% during the post-exercise period. A greater reduction of 50% of the basal insulin infusion rate during this post-exercise period was associated with elevated blood glucose levels.

The advent of commercially available continuous glucose monitoring (CGMS) equipment may seem to offer a significant advance in the management of exercise and T1DM. Unfortunately, the correlation between the CGMS measurements and capillary blood glucose is not reliable during exercise and is not yet a useful tool for identifying significant changes in glucose, and particularly hypoglycaemia, in real time. Current CGMS may have a role in alerting the user as to the trajectory and speed of fall of the glucose response to exercise. In contrast

<table>
<thead>
<tr>
<th>Adjustment</th>
<th>Endurance (aerobic exercise)</th>
<th>Intense (anaerobic exercise)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bolus dose insulin reduction</td>
<td>Useful when exercise occurs within 90 minutes of bolus dose</td>
<td>Not helpful, but may require additional bolus dose during or following exercise</td>
</tr>
<tr>
<td>Basal morning insulin dose reduction in multiple daily injection regimens before exercise</td>
<td>May be useful if on twice-daily basal injection, especially if exercise occurs less than every 3 days</td>
<td>Not helpful</td>
</tr>
<tr>
<td>Basal nocturnal insulin dose reduction in multiple daily injection regimens following exercise to reduce nocturnal hypoglycaemia</td>
<td>Useful especially if exercise occurs less than every 3 days</td>
<td>Useful especially if exercise occurs less than every 3 days</td>
</tr>
<tr>
<td>Altered continuous subcutaneous insulin infusion basal rate with exercise</td>
<td>Reduce basal rate to as low as 10% normal basal during exercise</td>
<td>Increased basal rate may be needed during exercise</td>
</tr>
<tr>
<td>Pre-exercise carbohydrate intake</td>
<td>Only if blood glucose &lt;8mM Typically 1g/kg/hr exercise up to 60g/hr</td>
<td>Not usually needed</td>
</tr>
<tr>
<td>Intra-exercise carbohydrate intake</td>
<td>Useful to reduce risk of hypoglycaemia and fatigue, with reduced dose of insulin</td>
<td>Not usually needed</td>
</tr>
<tr>
<td>Post-exercise carbohydrate intake</td>
<td>Will help reduce hypoglycaemia</td>
<td>Useful to reduce risk of hypoglycaemia and fatigue, with reduced dose of insulin</td>
</tr>
<tr>
<td>Pre- or post-exercise sprint</td>
<td>May reduce hypoglycaemia during or following exercise</td>
<td>May increase hyperglycaemia Unlikely to be helpful</td>
</tr>
</tbody>
</table>

Table 3. Strategies to promote euglycaemia during and following exercise
to the difficulties experienced with the accuracy of CGMS values during exercise, a further development of technology offers the possibility of reduction in hypoglycaemia following exercise. In one study, a sensor-augmented insulin pump system was equipped with an automatic suspension of insulin delivery with exercise-induced hypoglycaemia. The low glucose suspend (LGS) feature stops insulin delivery for 2 hours following a sensor glucose value ≤3.9 mmol/L (70 mg/dL). People with T1DM exercised until their plasma glucose value reached ≥4.7 mmol/L (85 mg/dL). When exercise sessions were done with the LGS feature turned on, the mean nadir and end glucose values were higher than when the feature was switched off. Automatic suspension of insulin delivery significantly reduced the duration and severity of exercise-induced hypoglycaemia without causing rebound hyperglycaemia.40

Conclusions
Cycling in people with type 1 diabetes can produce large changes in blood glucose, with hypoglycaemia likely and hyperglycaemia possible during and following exercise. There have been significant recent improvements in the knowledge of what underlies these changes and in appropriate management to support the maintenance of euglycaemia.

With careful questioning of the type, timing, duration and intensity of cycling, detailed review of intake of food and timing of insulin injections, blood glucose control can be maintained. Nocturnal hypoglycaemia following exercise remains a concern, and planning is essential to reduce this risk. Further advances in insulin infusion pump therapy and continuous subcutaneous glucose monitoring are likely to be useful in the management of people with type 1 diabetes who want to exercise. With the support of a skilled clinician, there is no reason why people with type 1 diabetes should not be able to bike safely while maintaining good glycaemic control.

Declaration of interests
There are no conflicts of interest declared.

References