COMMENTARY

Handling Exercise During Closed Loop Control

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Introduction

PEOPLE WITH TYPE 1 diabetes mellitus (T1DM) are at continual risk for hypoglycemia, which is recognized as one of the principal impediments to optimal glycemic control.^{1,2}

Physical exercise in T1DM has been associated with many health benefits, such as reduced cardiovascular risks, and improved psychological well-being and possible benefits in bone health.^{3–5} However, exercise also leads to an imbalance between hepatic glucose production and glucose disposal into muscle,⁶ increased insulin sensitivity related to glucose transporter type 4 translocation upregulation, and impaired counterregulatory hormonal response.^{7,8} In the absence of sufficient insulin reduction and/or carbohydrate supplementation, hypoglycemia often occurs during exercise, as well as during early and late recovery.^{9,10} Despite growing awareness of exercise benefits, fear of hypoglycemia often results in avoidance of physical activity¹¹ or in overcompensatory treatment behaviors leading to worsened metabolic control.¹² Exercise has also been shown to mask hypoglycemic symptoms, thereby facilitating repeated exposure to unrecognized hypoglycemia and potentially causing hypoglycemia-associated autonomic failure⁸ with all its negative consequences.¹ As a consequence, many people with T1DM engage in less exercise than their nondiabetic counterparts.¹³ This finding is partly driven by patients' fear of hypoglycemia and lack of tools and/or knowledge on how to avoid hypoglycemic events.¹³

To harness the benefits of exercise, people with T1DM must therefore carefully balance insulin regimen and carbohydrate intake before, during, and after exercise bouts. Strategies for adaptation to exercise primarily involve adjustment of insulin regimen and carbohydrates intake, and decision support systems have appeared and have shown promises in avoiding immediate hypoglycemia.¹² Nonetheless, these are still in early development as noted in Robertson et al.¹⁴: “Currently, no evidence-based guidelines exist on the amount and timing of increased carbohydrate to limit post-exercise hypoglycemia. However, reductions in basal insulin, low glycemic index snacks (with no bolus), or reduced boluses at post-exercise meals will usually reduce the problem.”

Automated Adaptation to Exercise

As insulin shutoff has been shown to be beneficial to exercise control under some circumstances,¹⁵ closed loop control (CLC) systems have naturally been seen as a potentially significant step toward better glycemic control during and after physical activity.

CLC systems have been tested against a variety of glycemic disturbances and few have proven as challenging as physical activity. Physical activity has been used in two distinct ways in CLC study: (i) as a mean to increase insulin sensitivity and risk of hypoglycemia over several hours, especially at night, and therefore test the CLC capacity to appropriately reduce insulin injections and avoid slowly developing hypoglycemia,^{15–17} and (ii) as an acute metabolic disturbance, generating unpredictable changes in glucose levels associated with sharp and transient shift in glucose metabolism.^{18,19} For example, in a multisite study in both adolescents and adults, the international Artificial Pancreas (iAP) group showed reduced hypoglycemia almost three times overall and up to six times in the hours after an exercise bout and during the night afterward, but no change in hypoglycemia during exercise.¹⁸ These results indicate that naive (not informed of physical activity) CLC systems may be limited in their ability to ensure optimal control during hypoglycemia inducing physical activity (e.g., prolonged mild-to-moderate aerobic exercise). It is understandable that several CLC research groups focused on exercise informed systems; although the sources of additional information varied, manual announcement and automated detection through accelerometers, heart rate monitors, and other sensors have been tested.^{20–24} Improvement from exercise detection or *just in time* announcement were observed for both dual (glucagon–insulin) and single (insulin) hormone systems.

Interestingly, physical activity has also been a key element of studies aimed at demonstrating the safety and efficacy of artificial pancreas (AP) systems before their deployment in larger (>50 patients) and longer duration (>1 month) trials. Specifically, summer and winter camps have been key elements of the path to home AP use. The Boston University dual hormone system,²⁵ the University of Virginia system,²¹ the DREAM system,²⁶ and the Medtronic precursor to the

670G system²⁷ were tested in camp settings between 2013 and 2015, leading to large home trials a few years later, and in the case of Medtronic to the Food and Drug Administration-approved product. Systems continue to mature through this process as exemplified by a recent publication.²⁸ Most trials were relatively small (~20 patients), and participants were adolescents or young adults. The vast majority of these trials included appropriate control groups (independent groups or crossover designs), which allowed a clear analysis of the system performance. Most did not specifically address performance during activity, reporting daytime glucose control improvement instead. In the study by Huyett et al.,²⁸ control activity during free physical activity was specifically addressed, showing encouraging controller actions; unfortunately, the absence of a formal control session did not allow for further assessment of the controller's performance.

Conclusion

Physical activity remains the focus of several clinical trials, either as an unknown disturbance the CL must reject or as a detected/announced event it must adapt to. With current insulin pharmacokinetics and limitations shown by glucagon to protect against hypoglycemia during prolonged exercise, it is not surprising that exercise informed system have outperformed their naive equivalents, but it remains to be seen if such system will be practical. To borrow from Riddell et al. in their excellent 2016 review: "Therefore, for effective glycemic control, it is imperative that the AP device has the capacity to respond to varying modalities, intensities, and durations of PA. Having an exercise smart AP system may encourage persons with T1D to increase their PA which would lead to several positive contributions in the management of diabetes ..."²⁹

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