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Intense Exercise in Type 1 Diabetes: Exploring the Role of Continuous Glucose Monitoring

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Abstract

Development of the external artificial pancreas (AP) is anticipated to be incremental, starting with simple and progressing to more complex applications incorporating exercise periods of various duration and intensity. Most studies investigating the effect of exercise on glucose excursions in subjects with type 1 diabetes either explored moderate exercise, which exerts different effects compared to intense exercise, or did not adopt continuous glucose monitoring combined with frequent plasma glucose measurements. Such studies could provide vital information. Performance of continuous glucose monitors during intense exercise could be evaluated to a greater extent. Frequently sampled blood glucose would facilitate better understanding of the relationship between intense exercise and metabolic processes, providing helpful information to patients with type 1 diabetes, clinicians, and researchers involved in the development of the AP.

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Introduction

The artificial pancreas (AP), consisting of a continuous glucose monitor (CGM), a control algorithm, and an insulin pump, is the subject of much research benefiting from advances in CGMs and reflecting the need for improved glucose control in subjects with type 1 diabetes. The AP is being developed to serve as a bridge to "cures" exemplified by stem cell therapy or other biologically based insulin replacement techniques.

Since the AP will be operating in diverse physiological conditions, a fully automated operation of the AP may not be possible at all times. Glucose excursions during highly dynamic conditions, such as following meal intake, are more difficult to control because of delays originating in the absorption of subcutaneously administered insulin.[1] A preemptive user-triggered delivery of the prandial bolus may be required. Conversely, exercise may require a preemptive modification of insulin delivery.

Currently marketed or close-to-market CGMs have proven useful in highlighting periods of hyper- and hypoglycemia. However, their use during exercise, particularly during intense exercise, has been limited. CGMs not only could facilitate investigations of various types of exercise in well-controlled environments, but also in daily life conditions, providing valuable information to subjects with type 1

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Abbreviations: (AP) artificial pancreas, (CGM) continuous glucose monitor

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diabetes, clinicians, and AP developers. Results from studies that used CGMs during exercise have been encouraging.[2–5] However, further studies are required to assess CGM accuracy over a wider spectrum of exercise intensity in both laboratory and ambulatory conditions with subjects entering competitive activities and prepared to use concomitantly traditional home glucose meters. First, this would assess whether CGM data are accurate, as controversies related to the reliability of CGMs prevail under such conditions. Second, such data could be used to ascertain that existing physiologically based mathematical models are able to describe intense exercise and, if necessary, to refine or develop adequate glucoregulatory models. Finally, computer simulations could be used to test control algorithms and assess their ability to achieve safe and efficacious glucose control during exercise of various intensities.[6]

Exercise is generally seen as a risk factor for acute and delayed hypoglycemia. This is well supported by numerous studies employing low-to-moderate exercise intensity.[7–9] However, in real life, repeated bouts of intense exercise ($VO_2 > 80\%\ VO_2$ max) are likely, especially in young active subjects and athletes. Exercise is often described as of high intensity despite a relatively low workload; the pronounced difference in the consequences on glucose concentration between low and very intense exercise calls for rigorous attention to the level at which exercise should really be considered as intense. Opposed to low and moderate exercise, intense exercise can lead to a substantial glucose rise. It has been suggested that this is because of a rise in catecholamines.[10–12] A reduced glucose utilization has also been suggested.[13] Several studies have demonstrated hyperglycemia during and following intense exercise in subjects with type 1 diabetes.[14,15] Hyperglycemia as a consequence of this type of exercise can be pronounced and prolonged,[16] especially if the subject follows the current recommendations of lowering insulin infusion and/or combining the preexercise period with carbohydrate intake.

More recent publications have confirmed the different outcome of moderate versus intense exercise following detailed studies employing glucose tracers during a euglycemic clamp.[17] However, the studies did not use CGMs and did not reflect real-life glucose dynamics because they relied on glucose infusion rather than food intake,[8,17] limiting their use for modeling purposes.

For a rational approach to modeling and simulation, exercise conditions should therefore be considered to be at least twofold and broken down into different studies, possibly leading to different models and different simulated tests. Previous work indicated that many factors can influence which category a particular exercise activity will fall into. A similar absolute workload can lead to substantial differences depending on the fitness level of the subject.[10,13] At an equal relative workload, large differences can also occur, and several studies have suggested that these are because of differences in stimulating the adrenal medulla, with trained athletes developing the so-called "sport medulla." In healthy trained athletes, the glucose elevation is more pronounced than in untrained individuals, as demonstrated clearly in a study by Kjaer and colleagues.[10] Although marginally less pronounced, this phenomenon may also be present in type 1 diabetes.[18] Trial designs for exercise studies should therefore include a careful selection of subjects.

The immediate danger of hypoglycemia has blunted the assessment of the consequences of intense exercise, which has been reported to have no effect on the risk of early hyperglycemia.[19] The intense exercise effect to elevate glucose is poorly quantified, and the prevalence of the phenomenon in the active population has not been evaluated. The potential hyperglycemic effect of intense exercise, although remaining to be fully quantified, has been used to assist subjects with type 1 diabetes in preventing hypoglycemia that often follows low-to-moderate exercise. The method consists of a series of sprints (high intensity activity) at the end of a low-to-moderate exercise session. However, as intense exercise seems to require $VO_2 > 80\%\ VO_2$ max, the method is clearly not adequate for all subjects.[20]

Postexercise hyperglycemia is physiological and may be required along with hyperinsulinemia during the recovery process to promote glycogen repletion. However, this may increase the subsequent risk of developing severe hypoglycemia in subjects with type 1 diabetes. Conversely, a lack of insulin may lead to sustained hyperglycemia, making the exercise deleterious to the patient in the long term if he/she engages in regular intense activities. Replicating the hyperinsulinemia associated with intense exercise as seen in healthy subjects could represent a challenging problem for the AP because of the frequent risk of hypoglycemia.[7]

Studies combining CGMs and targeting intense exercise could help raise awareness and provide clinicians and type 1 subjects with information about glucose dynamics not only before and after but also during exercise and/or intense exercise, allowing for appropriate adjustments. Although the CGM may not provide accurate values, it may at least indicate the

trend, and combining this information with an estimate of insulin onboard could facilitate the optimization of insulin adjustments before, during, and after the exercise session. For competing athletes, understanding the phenomena could help improve competitiveness by reducing the risk of dehydration which could be caused or aggravated by hyperglycemia.

As opposed to a spot glucose measurement, which does not provide information about the rate of glucose change, the CGM could be a very valuable tool. Provided that large-scale data sets can be collected (this would have cost implications) and population groups distinguished by their level of fitness and activity intensity, the prevalence and extent of intense exercise associated with hyperglycemia in type 1 diabetes could be estimated. It could lead to the refinement of recommendations for subjects engaging in physical activities, help identify at-risk population, understand individual's glucose changes, and safeguard more efficiently from hypoglycemia and hyperglycemia events. Ultimately this could induce a better management of hypoglycemia and the cumbersome fear associated with this event.[21]

Model predictive control algorithms are often favored when controlling systems with large delays such as that associated with the AP, but they depend on good predictive models. Additional experimental data could help develop or refine currently available glucoregulatory models. During physiological conditions of intense exercise, the glucagon-to-insulin ratio is not the main driving force of glucose production, and long-term training affects the stress-induced exercise glucose response. Glucose trace will not be sufficient to understand the underlying physiology, but the relationship between exercise and glucose excursions could be better understood. The availability of glucose trace and precise activity logs from exercise experiment would provide sufficient information to represent the variability induced by exercise, hence providing a test bed for exercise physiological condition testing. Typically, the ability of glucose controllers to mimic postexercise hyperinsulinemia and associated hyperglycemia profile as found in healthy subjects during intense exercise could be tested. This would ultimately extend the future potential of the AP, making it safer and more efficient by reducing glucose variability in an increased number of physiological conditions.

Conclusion

Intense exercise induces a significantly different physiological response than moderate exercise and this response may depend on the fitness level. The prevalence of hyperglycemia as a consequence of intense rather than low-to-moderate exercise is currently unknown. Although limited by accuracy and not fully evaluated during exercise, CGMs could provide the necessary information. The use of CGMs during intense exercise could also support the development of guidelines for subjects engaging in various types of exercise. Intense exercise might be limited to certain subject groups but may increase the health benefit of exercise. Data collected during such studies would facilitate the improvement of glucoregulatory models and development of the artificial pancreas.

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