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Modeling of glycogen resynthesis according to insulin concentration: towards a system for prevention of late-onset exercise-induced hypoglycemia in Type 1 diabetes patients

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Abstract

One of the major barriers for physical activity in type 1 diabetes (T1D) patients is the risk of exercise-induced hypoglycemia, in particular the late-onset one. The identification of the relation between glycogen resynthesis rate after an exercise and insulin concentration would allow the development of new predictive models. The aim of the present work was thus to investigate this relation in T1D patients. We recruited 8 T1D subjects which underwent two 24-h observational experimental sessions: complete rest and a 3-hours treadmill walk. Glucose and insulin concentrations were measured throughout the two sessions. Comparing the data collected in the two sessions, the net glucose uptake was calculated; positive values were suggestive of glycogen repletion while negative values suggested liver glycogen breakdown. A significant correlation ($r=0.742$, $p<0.001$) was observed between insulin concentration and net glucose uptake, with the negative values corresponding to time periods showing the lowest insulin concentrations. In conclusion, the present study preliminarily assessed the impact of insulin concentration on the risk of late onset hypoglycemia, which is the first step towards a comprehensive and personalized system for prevention of exercise-induced hypoglycemia in Type 1 diabetes patients.

Keywords: Physiological modeling; Type 1 diabetes; exercise; late-onset hypoglycemia; glycogen repletion.

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1. Introduction

Type 1 diabetes (T1D) is an autoimmune metabolic disease characterized by elevated blood glucose levels due to the destruction of pancreatic β cells. In this pathologic condition the complex physiological feedback systems regulating blood glucose levels in the body are compromised. Blood glucose concentration is maintained in a normal range by insulin administrations tuned according to self-monitoring.

Exercise is one of the pillars of the management of T1D being associated with reduced risk of cardiovascular disease, decreased daily insulin requirements and improved quality of life [1]. Exercise-associated glycemic imbalances during and after the physical activity, however, are often difficult to manage in this population. In particular, exercise induced hypoglycemia can be dangerous and represents the greatest barrier to regular physical activity in T1D subjects [2].

Over the last decade different approaches were proposed and tested for the prevention of exercise-induced hypoglycemia occurring in T1D people during the effort and/or just after it [3-6]. Some of the promising approaches take into account a series of patient dependent factors like exercise intensity, insulin concentration and sensitivity, and patient's fitness level among others [7-9].

A further challenge of exercise is that this risk of hypoglycemia is high not only during the effort but also for up to 31 hours after its end [10, 11]. This late-onset postexercise hypoglycemia is particularly concerning during nighttime because of the significantly higher incidence of overnight hypoglycemia after afternoon exercise (26%) compared with afternoon rest [12]. Furthermore, the use of continuous glucose-monitoring technology reveals that this high risk for nocturnal hypoglycemia after exercise may be related to the intensity of exercise [13].

The literature concerning the late-onset hypoglycemia is rather scarce [11]. Conversely, identification of the factors determining the risk of hypoglycemia following an exercise and of methods to reduce this risk is of paramount importance for T1D patients.

In healthy people, in the early postexercise period, glycogen depletion provides a strong drive for its own resynthesis, with the provision of ~1 g/kg body mass of carbohydrates optimizing the process [14]. This first phase of rapid glycogen repletion is independent of insulin, and is followed by a slower phase, lasting several hours, that is dependent upon the insulin level [15]. Conversely, in T1D patients, insulin concentration is not adapted physiologically to the body's needs, although the externally administered hormone continues controlling the glucose fluxes among the various body compartments, while exerting its usual metabolic effects [8]. No information is available in the literature regarding the impact of insulin concentration in determining the glycogen repletion after an exercise in T1D subjects. The identification of the relation between glycogen resynthesis rate after an exercise and insulin concentration would allow to develop new predictive models, thus, improving the systems for prevention of hypoglycemia also for the hours after the effort.

The aim of the present work was thus to investigate, in T1D patients, the relation between insulin concentration and glycogen resynthesis rate after an exercise, estimated by the whole-body glucose uptake.

2. Materials and methods

2.1. Study population

Eight T1D patients (4 Males, 4 Females) aged 35-59 years were included. The mean±SD body mass was 73±15kg; mean±SD stature was 170±9 cm. The mean±SD glycated hemoglobin (Hba1c), index of long-term illness control, was 7±1%. Inclusion criteria of patients were: diagnosis of T1D for at least 3 years, not affected by other chronic diseases and no evidence of diabetes complications contraindicating physical activity. Volunteers were informed of the nature, purpose, and possible risks involved in the study before giving their written consent to participate in this study. The study was approved by the Ethical Committee of the University of Udine and was conducted according to the principles expressed in the Declaration of Helsinki.

2.2. Experimental protocol and data acquisition

Patients underwent two 24-h observational experimental sessions: the first one was completely at rest, the second one included a 3-hours treadmill walk during the morning [16] which had the aim of decreasing the body's glycogen content (Fig. 1). The day before both sessions, patients were advised to maintain their usual diet and insulin regimen and to avoid the occurrence of hypoglycemic events by carefully controlling their blood glucose levels according to the usual self-management procedures.

In both experimental sessions, patients injected themselves, subcutaneously in the abdomen wall, their usual fast-acting insulin dose at 7:30, 13:30 and 19:30 and, just thereafter, consumed their usual breakfast, lunch and dinner, respectively.

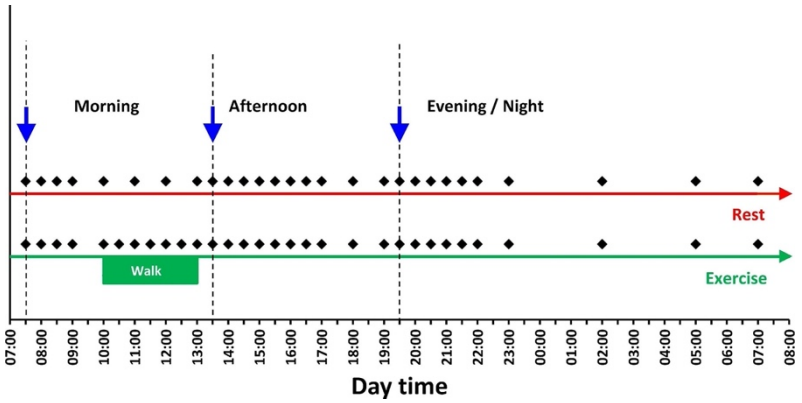

Fig. 1. Schematic representation of the experimental protocol. Black diamonds correspond to the time points of the blood withdrawals; blue vertical arrows indicate the time points of the meals (breakfast, lunch and dinner, respectively).

Volunteers were asked to arrive at the laboratory early in the morning. Immediately after breakfast, an indwelling catheter was inserted into each forearm vein of the subject, one for venous blood withdrawal, the other for glucose or insulin infusion, if needed; patency of the catheters was maintained by intermittent flushing with saline. Thereafter, apart from the exercise period, patients were allowed to sit quietly in an armchair (or lie in bed) and were kept under supervision of a physician and an expert nurse trained in diabetes.

Every 30 min in the 3 hours following the meals and at regular intervals in between (Fig.1), venous blood (~5 mL) was collected. A drop of it was used to immediately test glucose level by reactive strips (ContourLink, Bayer Healthcare Diabetes Division). In order to maintain glucose level in the range of 140-180 mg/dL in the 2 hours after the meals and 80-120 mg/dL in between, glucose or rapid-acting insulin infusion were used. All the amounts of glucose infused or of amounts of carbohydrates administered to the patients besides their usual diet were recorded. The insulin infusion periods performed during the first experimental session at rest were repeated identical during the second experimental session which included the exercise period.

The exercise consisted in a 3-h (from 10:00 to 13:00) constant heart rate walk on a treadmill (Saturn, H-P Cosmos, Traunstein, Germany). Target HR was kept constant by the treadmill through automatic adjusting of speed and/or slope. To minimize dizziness due to prolonged treadmill exercise, a 5-min rest were allowed at the end of each hour of exercise.

To counter an excessive fall of glycemia during exercise, the ECRES algorithm proposed by our workgroup was applied [5, 7, 17]. This algorithm estimates the overall amount of glucose burned (on average 107±23 g of carbohydrates), and, subsequently, calculates the amount of carbohydrates required by the patient according to his/her insulin concentration during the exercise. Accordingly, patients were given 60±23 g of sucrose distributed throughout the walk. The difference between the estimated amount of overall glucose burned and the amount required to avoid immediate hyopglycemia during the exercise can be assumed to represent an estimate of the

amount of glycogen burned during the exercise itself. In the present investigation it amounted on average to 47±8 g. All volunteers were allowed to drink water ad libitum.

2.3. Laboratory analyses of blood samples

The collected blood was divided into a 2-mL Vacutainer tube (#368920) containing a glycolysis inhibitor (4 mg of kalium oxalate + 5 mg of sodium fluoride) and a 3.5-mL Vacutainer SST™ II advance tube (#368965) with gel and clot activator. Immediately thereafter, both the tubes were gently inverted and stored at +4°C until the hospital laboratory centrifuged the samples to separate serum and perform the measurements. Plasma glucose concentration was determined by applying a hexokinase-based methodology (Olympus Diagnostic Systems AU2700; coefficient of analytical variation <2% in the range 60-210 mg/dL). Insulin concentrations were determined by means of the Beckman Access 2 Automated Immunoassay system (Beckman Coulter, Fullerton, CA; coefficient of analytical variation <6% in the range of 73.9-327.5 pmol·L-1). This analytical method measures all the relevant insulin analogs showing a cross-reactivity of about 80% [18].

2.4. Data analyses

The rate of glycogen resynthesis repletion was estimated by comparing the blood glucose levels of the experimental session including the exercise to those obtained in the session at rest, after their conversion in absolute quantities by taking into account the volume of the patient's extracellular fluid (ECF). Indeed, it can be hypothesized that the patient's glycemic profile will be overlapping after identical insulin administrations and consumed meals in two subsequent days. Accordingly, for each time period between two consecutive blood withdrawals, the net glucose uptake was calculated as follows:

$$NetGlu = \frac{\left(\left(GluEx - Glu\,\mathrm{Re}\right) + CHO\right)}{t} \tag{1}$$

where NetGlu (g/min) is the net glucose uptake, assumed to represent the glycogen repletion rate, GluEx and GluRe are the glucose levels (mg/dL, converted to grams on the basis of individual's ECF) during the exercise and the resting sessions, respectively, CHO (g) is the amount of carbohydrates administered (or glucose infused) besides the usual diet, and t (min) is the duration of the time elapsed between the two consecutive blood withdrawals.

Notably, positive values of NetGlu correspond to a greater glucose uptake after the exercise, which is suggestive of a greater glucose disposal due to repletion of glycogen stores. Conversely, negative NetGlu values suggest a glucose release in the bloodstream, likely due to liver glycogen depletion.

Analysis of variance (ANOVA) for repeated measurements was applied to detect significant differences among the glucose, or the insulin, levels in the two experimental sessions. Correlation between NetGlu and average insulin concentration was investigated through the Pearson correlation coefficient. A $p < 0.05$ was considered statistically significant. A $p < 0.05$ was considered statistically significant.

3. Results

The average venous blood glucose concentrations throughout the two experimental sessions are illustrated in Fig. 2. No significant difference was observed between the two sessions (ANOVA, session effect, p= n.s. - not significant). The glucose levels were maintained quite well within the required thresholds during both experimental sessions.

Fig. 3 illustrates the venous blood insulin concentrations throughout the two experimental sessions; no significant difference was observed between the two sessions (ANOVA, session effect, p= n.s.).

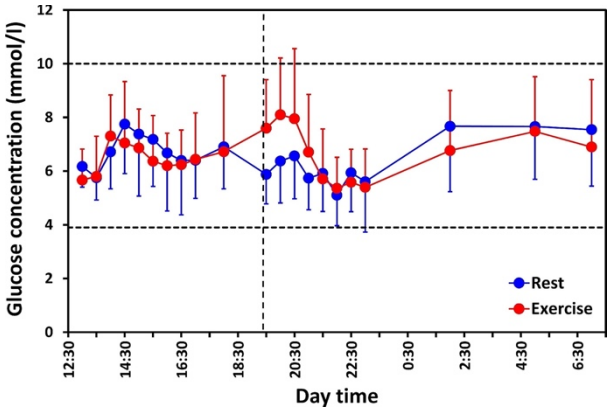

Fig. 2. Venous blood glucose concentration throughout the two experimental sessions. The horizontal dashed lines represent the clinically acceptable thresholds. The vertical dotted line corresponds to the time when dinner was administered to the patients.

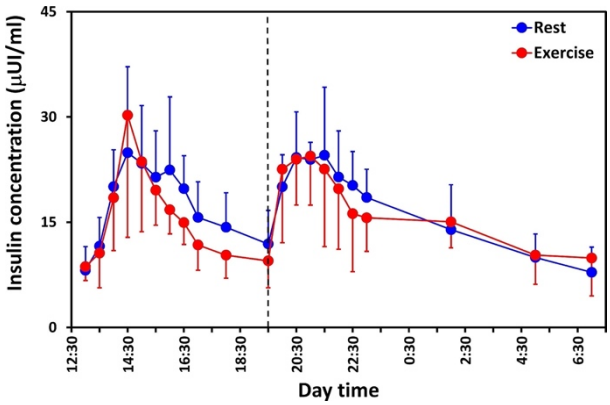

Fig. 3. Venous blood insulin concentration throughout the two experimental sessions. The vertical dotted line corresponds to the time when patients injected themselves the insulin bolus for dinner, which was then administered.

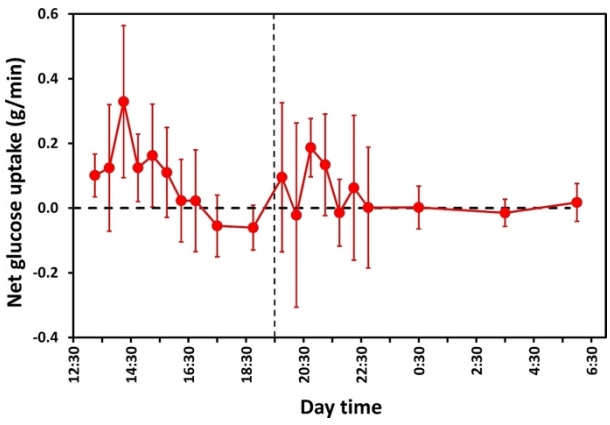

Fig. 4. Average difference in glucose uptake rate as a function of time. The vertical dotted line corresponds to the time when dinner was administered to the patients.

The average net glucose uptake is illustrated in Fig. 4 as a function of the day time. The net glucose uptake showed two main positive peaks, both just after the meals and one negative peak about 3 hours after lunch. For each subject, the sum of the extra glucose uptake from lunch to dinner (i.e. from 13:30 to 19:30), i.e. the overall amount of glucose disposal, corresponded to 69.8±24.7% of the amount of glycogen depleted during the 3-h walks. Considering the same time period, the average net glucose uptake rates were significantly correlated to the corresponding average prevailing insulin concentrations ($r=0.742$, $n=10$, $p<0.001$; Fig. 5). To be noted that the negative net glucose uptakes corresponded to time periods where the lowest insulin concentrations were observed, that likely allowed for liver glycogen depletion. This phenomenon might influence, so far to an unpredictable extent, the net glucose uptake during the evening. Nevertheless, taking the whole observation period until the next morning, the significant correlation between the average NetGlu and average insulin concentration is maintained, although becoming slightly less significant ($r=0.658$, $n=20$, $p<0.005$).

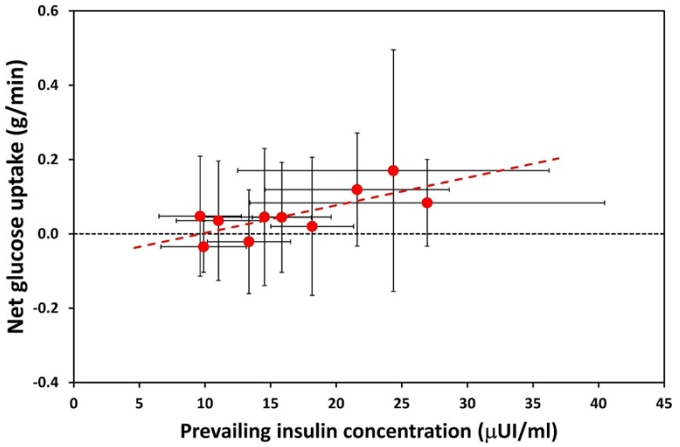

Fig. 5. The average difference in glucose uptake rate is represented as a function of the prevailing insulin concentration during the corresponding time periods. The two parameters were linearly related.

4. Discussion

Personalized patient-oriented strategies and technology solutions should be developed to support self-empowerment of chronic patients [19]. In T1D patients the risk of exercise-induced hypoglycemia still represents a great barrier towards regular moderate intensity physical activity [2]. Therefore, personalized strategies should be developed using also mHealth technologies to overcome the aforementioned hazard and support self-management [20].

In order to develop a model which could contribute to the prevention of post-exercise hypoglycemia it is of key importance to assess the dependency of glycogen repletion after exercise on insulin concentration in T1D subjects. We found a significant moderate correlation between insulin concentration and glycogen resynthesis, preliminarily assessed in this study for the first time.

The observed relationship suggests that the periods just after the meals, when patients administer themselves the fast-acting insulin bolus, are at great risk of late-onset hypoglycemia. In the meanwhile, the frequent observation of an excessive fall of glycemia during the night after an exercise might be linked to the increased insulin sensitivity during this day period [21], that metabolically has an effect similar to an increased insulin concentration.

The large standard deviation of each time period suggests a great interpersonal variability in this relationship, that might be due to different insulin sensitivity among the observed patients. Indeed, there is evidence that physical activity can affect insulin sensitivity up to 48 hours [22]. Therefore, insulin sensitivity is one of the factors that

should be taken into account in the modelling for the prevention of exercise-induced hypoglycemia [8], even so for the late-onset one.

Our findings allow future improvement of the systems for prevention of hypoglycemia, such as ECRES, making them efficient also for the hours following the effort. In Figure 6 is presented the hypothesis for the adaptation of the ECRES system (Panel B), in order to also prevent the risk of late-onset hypoglycemia on the basis of this paper findings. The original ECRES system (panel A) is described in detail in a previous study [5]. Briefly, the ECRES algorithm calculates CHO required before/during the activity (CHOpre) based on patient and exercise -specific data, as well as CHO required after the exercise (CHOpost). The identified dependency between insulin concentration and glucose uptake allows to estimate the distribution of this required uptake (CHOpost) over time, taking into account also the patient's specific insulin daily profile.

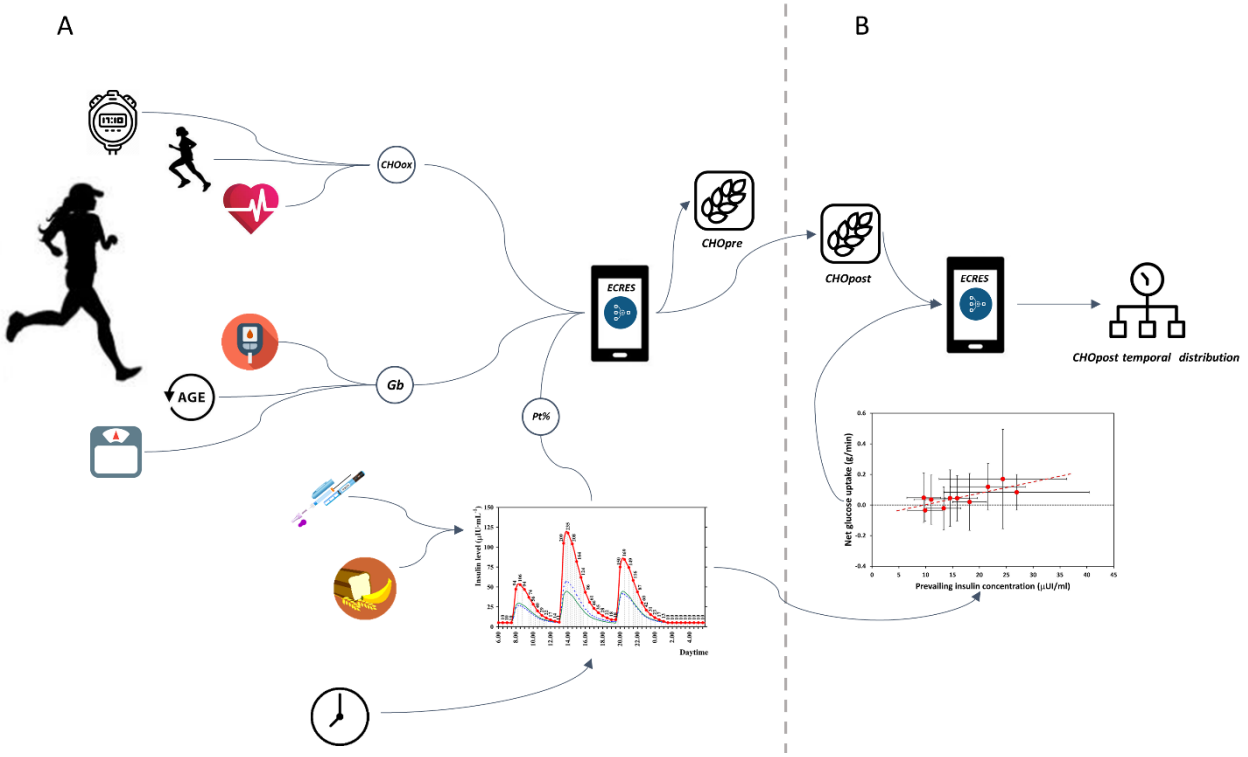

Fig. 6. Schematic representation of the remodeled ECRES system. Panel A - The original ECRES system. The following data have to be provided as inputs to obtain CHO estimates (from top bottom): (1) duration foreseen for the specific exercise, patient's fitness level and average heart rate; (2) capillary blood glucose level measured just before the start, age and weight; (3) patient's usual therapy (i.e., insulin types, doses, and time scheduling, together with the dietary carbohydrates) and time of day of exercise. The ECRES algorithm estimates the amount of carbohydrates supplement required before/during the activity (CHOpre) as a percentage (Pt%) of the total amount of carbohydrates burned during the exercise (CHOox) corrected by the excess or lack of glucose contained in the extracellular fluid compartment (Gb), as well as CHO required after the exercise (CHOpost). Panel B – Adaptation of ECRES system. The identified dependency between insulin concentration and glucose uptake allows to estimate the distribution of required uptake (CHOpost) over time, taking into account also the patient's specific insulin daily profile.

In conclusion, the present study preliminarily assessed the impact of insulin concentration on the risk of late onset hypoglycemia, which is the first step towards a comprehensive and personalized system for prevention of exercise-induced hypoglycemia in Type 1 diabetes patients.

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Conflict of interest

The authors have no conflict of interest do declare.

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